SYNTHESIS OF AMPHIPHILIC DITHIENYLETHENES

A Thesis

Submitted to the Faculty of Graduate Studies and Research

In Partial Fulfillment of the Requirements

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In Chemistry

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By

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UNIVERSITY OF REGINA

FACULTY OF GRADUATE STUDIES AND RESEARCH

SUPERVISORY AND EXAMINING COMMITTEE

Mary Sally Jemeli Sang, candidate for the degree of Master of Science in Chemistry**,** has presented a thesis titled, ***Synthesis of Amphiphilic Dithienylethenes,*** in an oral examination held on October 24, 2017. The following committee members have found the thesis acceptable in form and content, and that the candidate demonstrated satisfactory knowledge of the subject material.

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Abstract

The work presented in this thesis describes the design and preparation of asymmetrical, amphiphilic dithienylethenes (DTEs). In general, enhancing the photochromic properties of DTEs is crucial to their application in biocompatible drug delivery systems. The syntheses of DTEs **1**–**4** were carried out following various devised synthetic routes. Within these synthetic routes, the efficiency of two coupling reactions was found to be important to the overall efficiency of these syntheses. The first reaction involved the regioselective substitution at the 2– and 5–position of thiophene derivatives with aryl- and alkylaryl-substituted boronic acids via Suzuki–Miyaura cross-coupling reactions. In most cases, these substitution reactions were successful in moderate yields. Secondly, lithium-halogen exchange reactions were used to generate the 3-thienyllithium intermediates that were then coupled to mono-substituted perfluorocyclopentene derivatives via a nucleophilic addition–elimination reaction. The efficiency of this coupling reaction was greatly influenced by the nature of substituents at the 2–, 2'–, 4–, 4'– and 5–, 5'–positions of the thiophene ring systems. The synthesis of **1** and **3** and intermediate products for **2** and **4** were successfully prepared. However, the final coupling reaction used to prepare the precursors of **2** and **4** was unsuccessful. It was concluded that the preparation of **2** and **4** would be viable if the scale of these synthetic routes was increased ten fold.

Acknowledgements

I am genuinely thankful to my supervisor, Dr. R. Scott Murphy who has been a great mentor in many aspects of life. I truly appreciate Dr. Murphy's patience, guidance, advice and the support he provided throughout my graduate studies. The training I received in his research group has helped me develop better research, teaching and writing skills.

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Dedicated to:

My Parents

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List of Abbreviations and Symbols

br	broad
bpy	2,2'-bipyridyl
n-BuLi	*n*-butyllithium
c	closed-ring isomer of DTE
calcd	calculated
d	doublet
dd	doublet of doublets
dba	dibenzylideneacetone
DTE	dithienylethene
EI	electron ionization
FD	field desorption
HRMS	high-resolution mass spectrometry
J	coupling constant
n-BuLi	*n*-butyllithium
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
m	multiplet
m/*z*	mass-to-charge ratio
o	opened-ring isomer of DTE
OFCP	octafluorocyclopentene
PSS	photostationary state
R_f	retention factor

rt	room temperature
s	singlet
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
UV	ultraviolet
vis	visible
δ	NMR chemical shift in parts per million
ν	frequency of light
Φ	quantum yield
Φoc	photocyclization quantum yield

1.0 Introduction

1.1 Diarylethenes

Diarylethenes are a class of photochromic compounds that undergo reversible, light-induced isomerization between an open-ring isomer and a closed-ring isomer.[1,2] Diarylethenes are classified as P-type photochromic compounds because the cyclization/cycloreversion reactions can only be driven by light. Another class of photochromic compounds that include azobenzene and spiropyran are termed T-type because their photochromic reactions are thermally reversible.[2,3] The general structure of diarylethenes is comprised of a 1,3,5-hexatriene core highlighted in bold in Figure 1.1. The compound is made up of two heteroaryl groups connected at the 3– and 3'–positions to a central alkene.

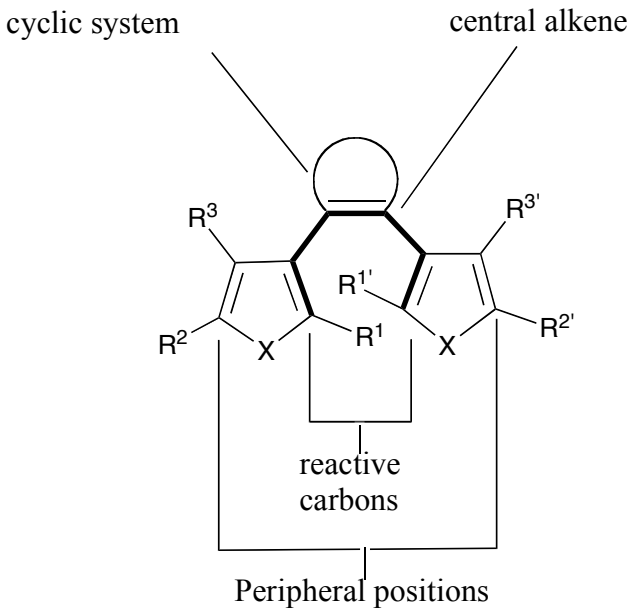


Figure 1.1 The basic structure of a diarylethene.

The heteroaryl groups can either be a fused ring system (e.g., benzothiophene and benzofuran) or a 5-membered ring such as thiophene, furan, and oxazole.[1,3] Diarylethenes incorporating thiophene rings are specifically termed dithienylethenes (DTEs). If the DTE structure lacks the cyclic alkenyl backbone, the open-ring isomer excited state may undergo a competing Z → E isomerization reaction.[2] Therefore, a central cyclic alkene such as a cyclopentene or hexafluorocyclopentene is required to prevent the rotation of the groups attached to the alkenyl bond. The 2– and 2'–positions, generally called the reactive carbons, are often substituted with alkyl or aryl groups to enhance reversibility and prevent oxidative aromatization of the closed-ring structure.[1,2] Moreover, the substituents on all positions (R^1–R^3) can be modified to alter the photochromic behavior of the isomers to fit the desired application.[1]

1.2 Photochromic reactions of DTEs.

The reversible photochromic reactions of DTEs are based on the cyclization of the 1,3,5-hexatriene core and the ring-opening of a 1,3-cyclohexadiene derivative.[1,4] The open-ring isomer (**DTE-o**) often absorbs electromagnetic radiation in the ultraviolet (UV) region and undergo a 6 pi (π) electrocyclization reaction to give a closed-ring isomer (**DTE-c**; Figure 1.2A).[5] During this ring closure reaction; a sigma (σ) bond is formed, at the expense of a π bond, between the termini of a conjugated 1,3,5-hexatriene (Figure 1.2B). The electrocyclic reaction of DTEs is highly stereospecific and the stereochemistry of the product is predicted by the Woodward-Hoffmann rules.[6] According to these rules, an electrocyclic reaction of a 6π-electron system proceeds via a

conrotatory rotation under photochemical conditions. As a result, the substituents at the reactive carbons are *trans* to one another about the plane of the ring system (Figure 1.2C).[6] The photoisomerization reaction from **DTE-o** to **DTE-c** is accompanied by a change in the absorption spectrum. Often, a visible colour change is observed because the closed-ring isomer has an extended π-conjugated system, with an absorption that spans both the UV and the visible region of the spectrum.[7]

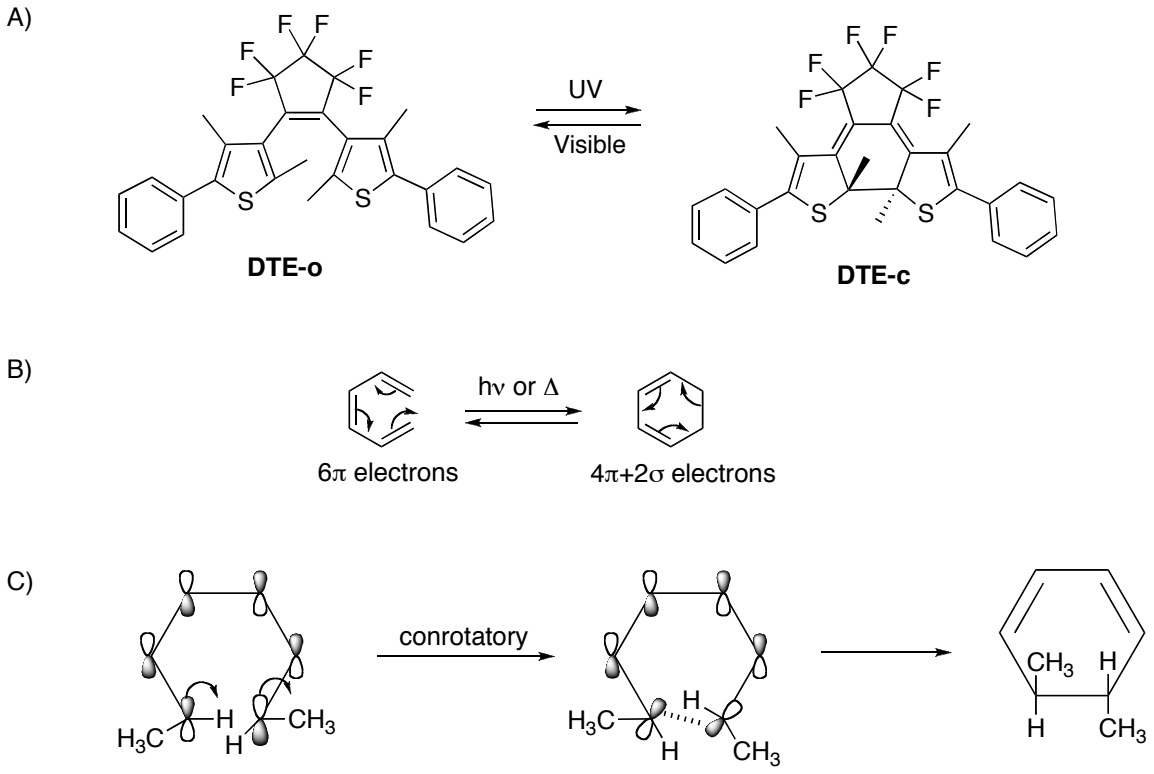


Figure 1.2 Photochromic reactions of DTEs. A) Reversible photoconversion between the open-ring isomer (**DTE-o**) and the closed-ring isomer (**DTE-c**), B) A 6π-electron rearrangement in 1,3,5-hexatriene to give a 1,3-cylcohexadiene, C) Overlap of *p* orbitals to form a σ bond via conrotatory mode (Adapted from reference 5).

The DTE closed-ring isomer can be reverted back to the open-ring isomer by exposure to another wavelength of light, typically in the visible region. Generally, the majority of DTE isomers are considered to be thermally stable with minimal cycloreversion even at high temperatures. The closed-ring isomers of most DTEs remains cyclized in the dark for > 3 months at 80 °C.[1,8] As a result, these DTEs are attractive because one can achieve a complete photocontrol over the isomeric state.[9]

Apart from the electronic structural changes that accompany DTE photoisomerization, the geometrical structure of the DTE also changes.[3,10] Photocontrol of these structural changes at the molecular level is useful in a range of applications. For instance, the electronic structural changes can be applied to optical information storage, molecular electronics, and photonic devices.[11–14] On the other hand, the geometrical changes have gained interest in biological applications that include photoresponsive self-assemblies,[15,16] catalytic functions,[17] and super-resolution imaging.[17,18] The utility of DTEs can be improved if they display some sought-after properties such as high fatigue resistance,[20,21] and a short response time (i.e., picosecond time regime).[21–23] While these photochromic properties are important for the DTE applications, there are few DTEs that meet all of these specifications. Thus, the overall objective of this research is to design and synthesize asymmetrical amphiphilic DTEs that incorporate structural features that will improve photochromic properties and lipid complementarity. In the future, we aim to incorporate these DTEs in lipid vesicles to produce photoresponsive self-assemblies. Hence, the asymmetrical and amphiphilic nature of DTEs is important to improve their organization in the lipid vesicles.[15,16]

1.3 Substituent effects on photochromic properties of DTEs

1.3.1. Fatigue resistance

DTE compounds have attracted great attention in recent years due to their advanced photochromic properties.[1,8,9] Improving DTE reversibility is a fundamental goal with regards to their applications in many areas. DTEs with a high fatigue resistance are desirable because they can undergo many cyclization/cycloreversion reactions without experiencing significant chemical degradation and subsequent loss of their photochromic performance.[1] Fatigue is defined as the loss of reversibility between the closed-ring and the open-ring isomers following continuous photoirradiation. A slight occurrence of a side reaction that is barely observed when the photoisomerization is carried out only once can lead to a significant loss of the photochromic compound after many switching cycles.[1,20] It has been shown that continuous irradiation of DTEs can lead to the formation of a non-photochromic, irreversible photoproduct.[1,16,21] Figure 1.3 illustrates the formation of a photoproduct **c** from the closed-ring isomer of **a**. The photoproduct is thought to be formed via a rearrangement of thiophene rings in the closed-ring isomer.[20]

A recent theoretical study suggested that the most probable mechanism for the formation of the photoproduct is initiated by the photochemical cleavage of the C–S bond in one of the thiophene rings.[24] The C_1–S_8 bond length in the closed-ring isomer (1.829 Å) was found to be longer than a normal C–S bond (1.719 Å), which may facilitate bond cleavage in the photoexcited state.[24] This cleavage is then followed by a radical migration and formation of the C_1–C_5 bond, which gives a bicyclohexane intermediate **b**. Finally, cleavage of the C_5–C_6 bond leads to the formation of the irreversible fused ring

photoproduct **c**.

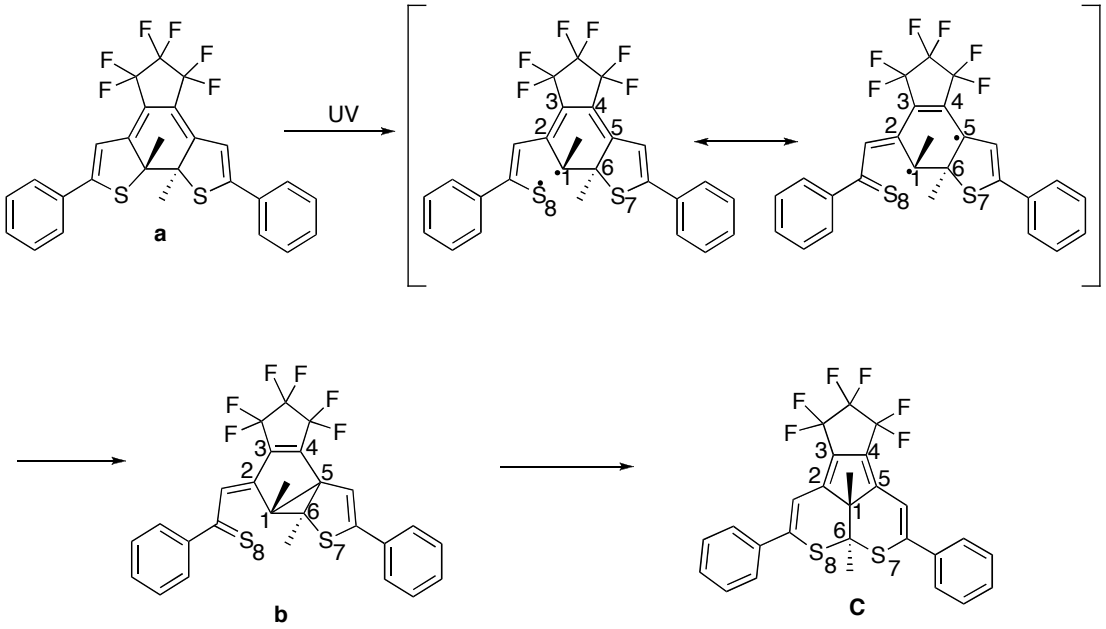


Figure 1.3 Formation of an irreversible photoproduct (**b**) from the closed-ring isomer of **a** (Adapted from reference 20).

Previous studies have shown that there are some correlations between the fatigue resistance behavior of a DTE and its molecular structure.[19,25-27] For example, Herder and coworkers noted that dithienylperhydrocyclopentenes suffer greater fatigue when compared to the respective dithienylperfluorocyclopentenes.[25] A recent study in our group also found that phenylethynyl substituents at the reactive carbons lower the fatigue resistance of DTEs by possibly increasing the stability of the radical intermediates through delocalization.[16] Furthermore, Jeong and coworkers reported that oxidation of one thiophene or benzothiophene unit to an *S,S*-dioxide may lead to improved fatigue resistance.[26] In addition to the above findings, Irie and coworkers reported that the

cyclization and cycloreversion cycles of perfluorocyclopentene derivatives with either a benzothiophene (1,2-bis(2-methyl-3-benzothienyl)perfluorocyclopentene) or methyl substitution at the 4– and 4'–positions (1,2-bis(2,4-dimethyl-5-phenyl-3-thienyl)perfluocyclopentene) shown in Figure 1.4 could be repeated many times without any significant degradation.[20] Substitution at the 4– and 4'–positions helps to suppress the excited-state pathway that leads to the formation of the irreversible photoproduct by introducing steric hindrance between the methyl groups and the fluorine atoms.[25] Therefore, the development of DTEs that incorporate methyl substituents at these positions is important for their utility.

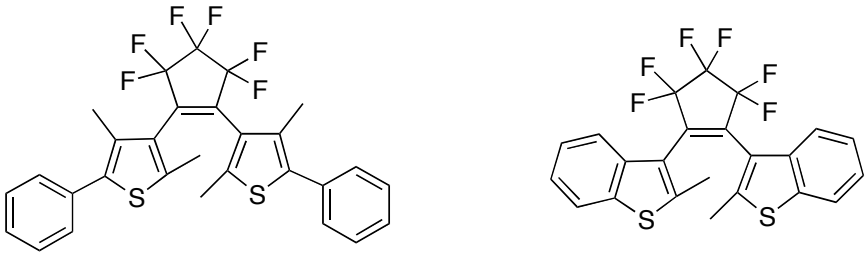


Figure 1.4 Examples of DTEs with high fatigue resistance.

1.3.2 Quantum yield

Highly efficient DTE photoisomerization reactions are necessary in order to attain full functionality in various applications. The photochromical efficiency of DTEs is determined based on the quantum yield. Quantum yield (Φ) refers to the ratio of the total number of molecules that isomerize to the total number of photons absorbed at a given wavelength.

$$\Phi = \frac{\text{Total \# of molecules that isomerize}}{\text{Total \# of photons absorbed}}$$

Equation 1.1 Quantum yield

DTE photocyclization quantum yields (Φoc) depend on the conformations of the open-ring isomer.[11] The open-ring isomer of DTEs has two possible conformations in solution; parallel (with mirror symmetry) and antiparallel (with C_2 symmetry).[11,16] These conformers exist due to the free rotation of C–C single bond between each of the thiophene rings and the cyclopentene ring (Figure 1.5).[8] The Φoc for most DTEs is limited to 0.5 because photocyclization can only take place from the antiparallel conformation. The antiparallel conformation favours photocyclization via a conrotatory mode.[8,11] Thus, it is important to promote the formation of the photoactive antiparallel conformation in order to achieve higher photocyclization yields.

There are several reported strategies aimed at promoting the antiparallel conformation. In one strategy, DTEs were mechanically locked into an antiparallel conformation by incorporating the photochromic unit into a polymer backbone.[29] This method however, is not easily applicable for small molecules. Alternatively, high Φoc (0.98) was achieved by incorporating hydrogen-bonding and sulfur-nitrogen interactions between the bridge unit and the aryl termini of the DTE solvents.[30] The main disadvantage associated with this strategy of directed non-covalent interactions is the solvent dependency, which was shown by varying Φoc in different solvents.[30]

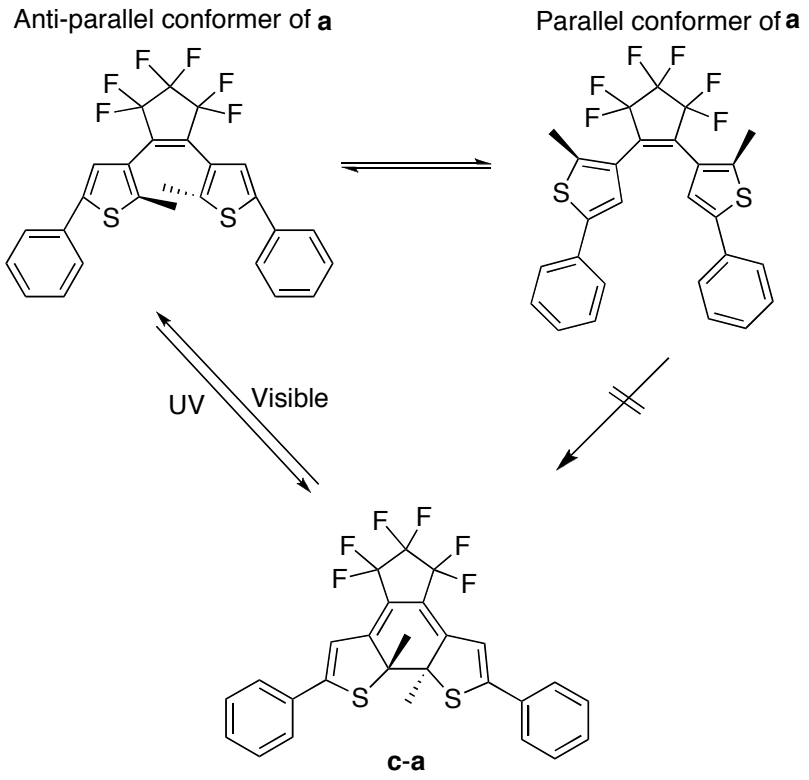
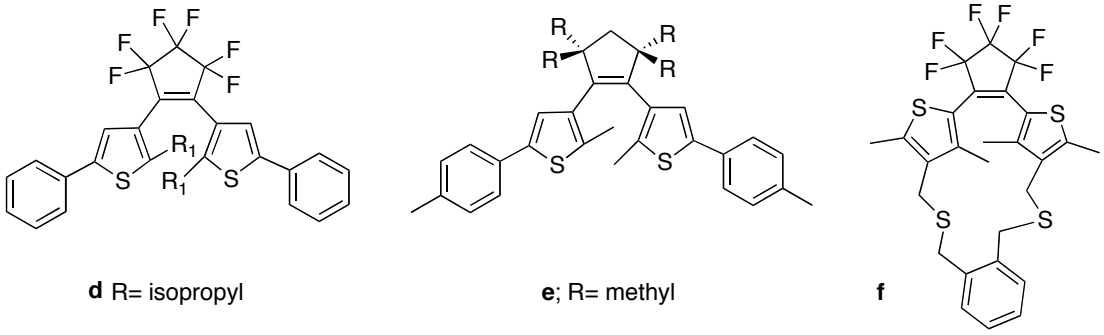


Figure 1.5 Photochemical cyclization of DTEs (Adapted from reference 9).

In contrast to the above, steric repulsion which is independent of the environment can be used to promote the formation of the photoactive antiparallel conformation. Sterically demanding substituents can either be introduced at the reactive carbon positions of the thiophene rings or at the ethene bridge (Figure 1.6). Irie and coworkers reported an example where substitution of methyl by bulkier isopropyl groups on the reactive carbons of **d** significantly increased the Φoc values from 0.31 to 0.52.[11,31] An increase in the Φoc can be observed when bulky substituents are present at the reactive carbon positions of thienyl rings because this increases the steric strain and decreases the ratio of the parallel conformer compared to the antiparallel conformer.[11] Gostl and coworkers reported a high Φoc value of 0.83 when four methyl groups were introduced

on the five-membered bridging ring of **e**.[32] Another study showed that linking the two aryl groups with an additional bridge at the *ortho* position of the reacting carbons as shown for **f** leads to increased Φoc.



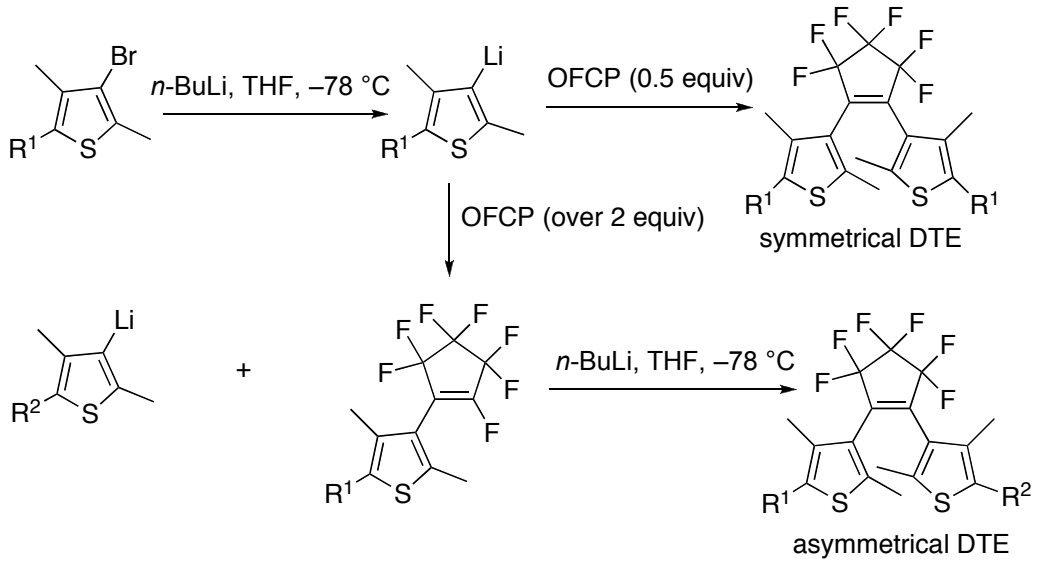
d R= isopropyl **e**; R= methyl **f**

F**igure 1.6** Examples of DTE derivatives that favour the antiparallel conformation.

1.4. General methods for preparation of DTEs

A great deal of work has focused on the development of new synthetic methods for the preparations of symmetrical and asymmetrical DTEs.[33-38] Several of these methods are discussed in this section. The most commonly reported method for the synthesis of symmetrical and asymmetrical DTEs that bear various aryl groups at the reactive carbons involve a formal substitution reaction where a preformed substituted thiophene is treated with lithium to form a substituted 3-thienyllithium intermediate. The 3-thienyllithium is then reacted with octafluorocyclopentene (OFCP) to give a mono- or di-substituted perfluorocyclopentene derivative (Scheme 1.1).[33-35] Specifically, symmetrical DTE derivatives can be obtained by reacting the thiophene derivative with a

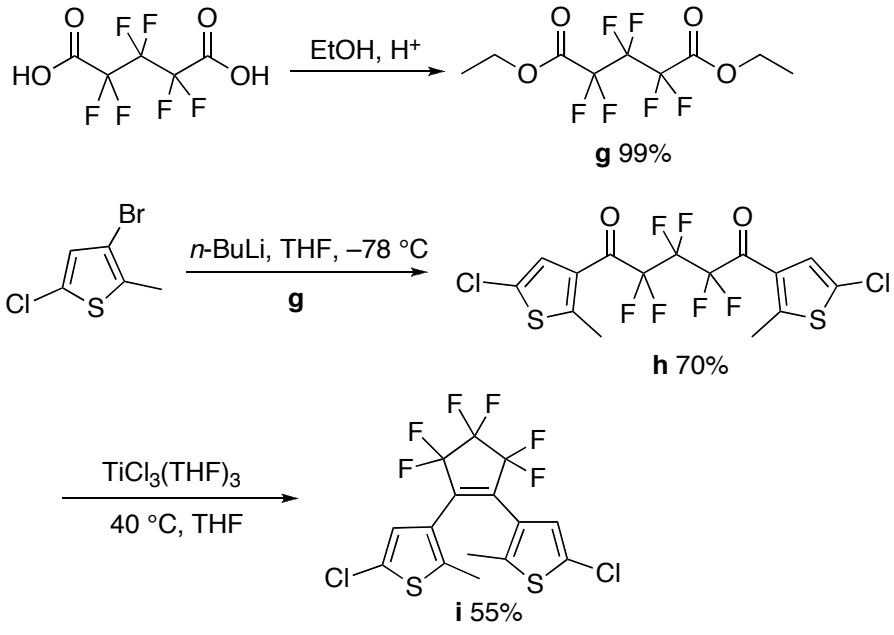
half mole equivalence of OFCP. Asymmetrical DTEs are also selectively prepared by controlling this ratio. Theoretically, using an equimolar ratio of OFCP ensures that only one of the fluorine atoms at the double bond of cyclopentene will be substituted leading to the formation of a mono-substituted product. In practice, an excess of OFCP i.e., 1:7 mole ratio, is generally used to account for any loses due to the high volatile nature of OFCP. Subsequent reactions with different lithiated thiophene derivatives under low temperature conditions afford asymmetrical DTEs.[39]



Scheme 1.1 Multi-step *n*-BuLi/OFCP synthesis of symmetrical and asymmetrical DTEs. (Adapted from reference 16)

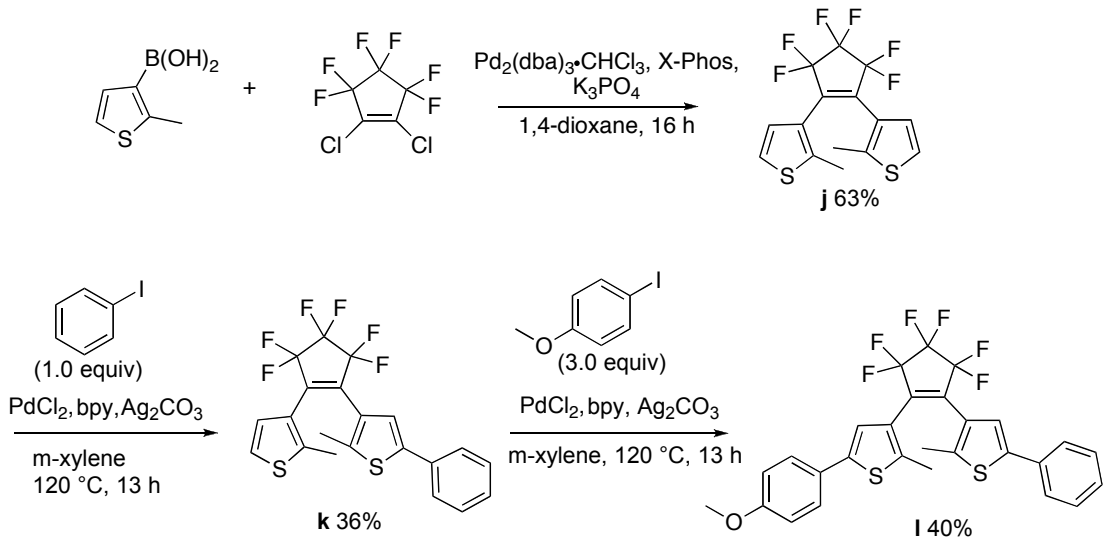
Another well-known method for preparing symmetrical and asymmetrical DTEs is based on an intramolecular McMurry cyclization reaction.[40] In this cyclization pathway, a central DTE backbone is initially prepared followed by functionalization of

the thiophene units.[41] The synthesis of these DTEs involves the conversion of hexafluoroglutaric acid into a 2,2,3,3,4,4-hexafluoro-1,5-diethyl pentanedioate (**g**). The ester is then coupled with a lithiated 3-bromo-5-chloro-2-methylthiophene to yield 1,5-bis(5-chloro-2-methyl-3-thienyl)-2,2,3,3,4,4-hexafluoro-1,5-pentanedione (**h**). A ring closure reaction of **h** gives the 1,2-bis(5-chloro-2-methyl-3-thienyl)-2,2,3,3,4,4-hexafluorocyclopentene (**i**). Different symmetrical and asymmetrical DTEs can then be synthesized with subsequent coupling reactions with various alkyl and arylbromides.[36,41,42] Compared to McMurry cyclization, the *n*-BuLi/OFCP method previously discussed is often preferred as it offers a regioselective approach that introduces functional groups at the periphery of the thiophene prior to the introduction of other substituents.



Scheme 1.2 Synthesis of **i** via McMurry cyclization (Adapted from reference 40).

Although the *n*-BuLi/OFCP approach allows for regioselective substitution on the thiophene, OFCP is highly volatile and expensive. Consequently, Shinokubo and coworkers proposed an alternative catalytic and non-cryogenic method for synthesizing DTEs.[43] The reaction uses 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene, which is less volatile and less expensive than OFCP. This method has been adopted in the synthesis of DTEs with different functional groups. For example, the reaction of 2-methyl-3-thienylboronic acid with 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene (Scheme 1.3) generated 1,2-bis(2-methyl-3-thienyl)-3,3,4,4,5,5-hexafluorocyclopentene (**j)** in moderate yield (63%). Further derivatization was required to allow for introduction of substituents on the thiophene rings.[43] A selective α-monoarylation on the thiophene moiety of **j** was achieved with one equivalent of iodobenzene to obtain a monoarylated product **k** (36%). Additional arylation of the monoarylated product with 1-iodo-4-methoxybenzene afforded asymmetrical DTE **l** (40%). This protocol allows for versatile functionalization of a simple DTE at 2–, 2'–, 4–, 4'– and 5–, 5'–positions of the thiophene rings and is suitable for thiophene with different functional groups.



Scheme 1.3 Synthesis of asymmetrical DTE by selective direct arylation of **l** (Adapted from reference 43).

1.5 Lithium-halogen exchange and formal substitution reactions of DTEs

To date, several research groups have successfully synthesized symmetrical and asymmetrical DTEs substituted at the reactive carbons (i.e., 2– and 2'–positions) and at the periphery (i.e., 5– and 5'–positions) of the thiophene rings.[33-38] On the other hand, very few asymmetrical DTEs bearing both methyl substituents at the 4– and 4'–positions and a bulky group at the reactive carbons have been reported.[44-48] This is despite the fact that these design principles are important to the photochromic performance of DTEs. The coupling yields of the available DTE examples are considerably low. In order to understand why this may be the case, it is important to discuss the mechanistic details of two important reactions in the *n*-BuLi/OFCP multi-step pathway commonly used in the synthesis of DTEs.

The initial lithium-halogen exchange reaction between aryl bromide and the *n*-BuLi results to the formation of a nucleophilic 3-thienyllithium intermediate. The conditions of lithium-halogen exchange play a major role in such reactions. These reactions are performed at low temperature (i.e., –78 °C) to help minimize other competitive side reactions such as Li–H exchange which can take place at temperatures of above –78 °C.[36] The next step is a nucleophilic addition-elimination on the sp^2-hybridized carbon of the perfluorocyclopentene derivative (Figure 1.7). The 3-thienyllithium intermediate forms a sigma (σ) bond with the electrophilic carbon and the pi (π) bond breaks to form a tetrahedral carbanion intermediate (hybridization changes from sp^2 to sp^3). Fluorine atoms in the ring system contribute to the stability of the intermediate through inductive effects. The last step is the reformation of the cyclopentene and the loss of the fluoride ion as a leaving group.

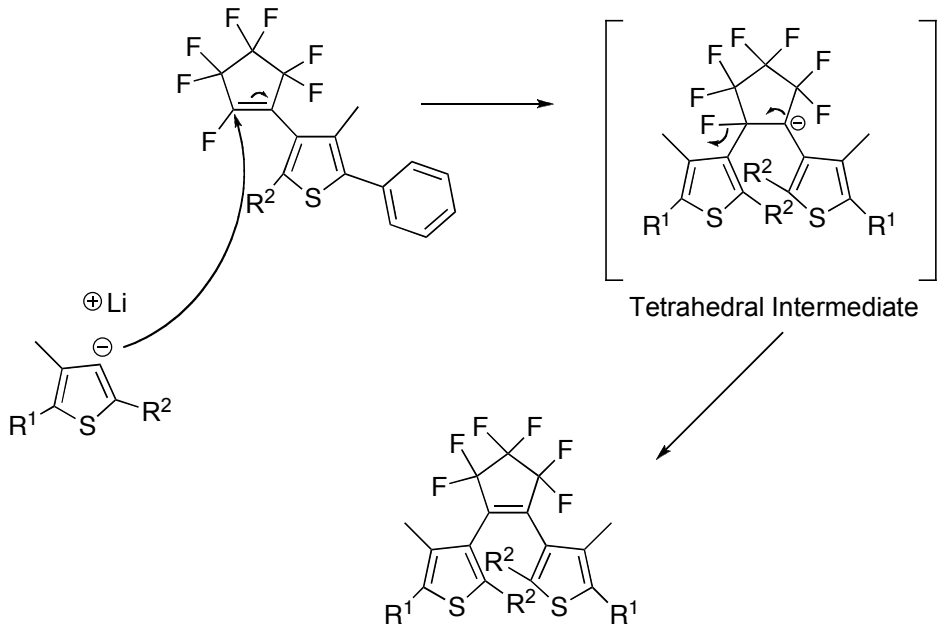
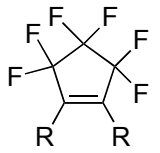


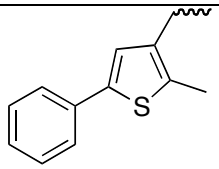
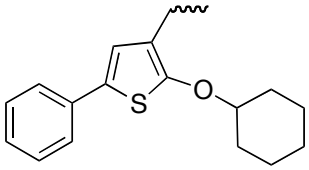
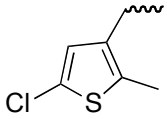
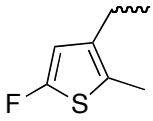
Figure 1.7 Addition–elimination mechanism for preparation of DTEs.

The overall coupling yields are highly dependent on the nature of the thiophene substituents. For instance, reactions with thiophenes bearing electron-withdrawing substituents are often low-yielding, while the presence of electron-donating or conjugative groups results in higher reaction yields. Additionally, the presence of a bulky group (i.e., bulkier than a methyl) on the thiophene has been shown to negatively impact the yields.[36]

Looking into the existing literature, a correlation between the overall reaction coupling yields and the nature of the substituents at the 2–, 2'–, 4–, 4'– and 5–, 5'– positions of the thiophenyl unit of DTEs was observed. Thiophenyl units bearing electron-donating groups tend to give increased DTE coupling yields. For example, Lee and coworkers synthesized 1,2-bis(2-methyl-5-phenyl-3-thienyl)perfluorocyclopentene reporting a yield of 38% (Table 1.1, entry 1).[48] Substitution of the weakly electron-donating methyl groups at the reactive positions with a more electron-donating cyclohexyloxy substituent showed a slight increase in the coupling yield to 44% (Table 1.1, entry 2).[34] On the other hand, electron-withdrawing substituents on the thiophenyl unit decreases the coupling yield (Table 1.1, entries 3 and 4).[36] This is because electron-withdrawing groups on the 3-thienyllithium carbanion decreases its nucleophilicity, therefore lowering the coupling efficiency.

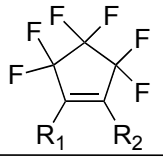
Table 1.1 Electronic effects on the coupling reactions of DTEs

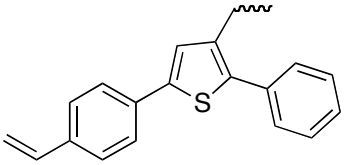
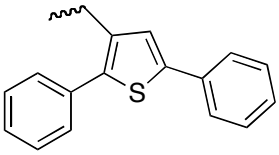
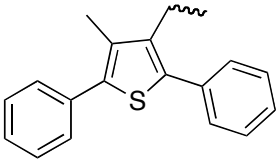
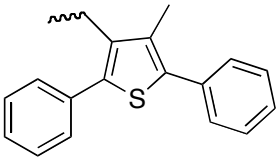
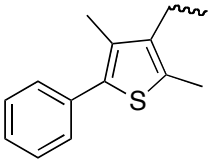
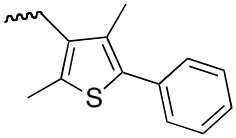
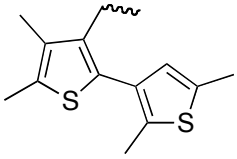
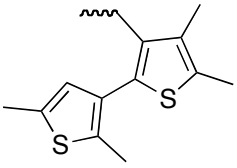


Entry	R	% Yield
1		38
2		44
3		27
4		16

Similarly, low DTE yields are reported when the perfluorocyclopentene derivative is reacted with 3-thienyllithium intermediate bearing bulky substituents at the reactive carbon positions. As shown in Table 1.2, there is a decrease in coupling yield from 45% to 17% when methyl substituents are introduced at the 4– and 4'–position of DTEs with bulky phenyl groups at the reactive carbons (Table 1.2, entries 1 and 2).[46] Substitution of the bulky phenyl ring at the reactive position with a methyl shows an increase in coupling yield from 17% to 44% (Table 1.2, entry 3).[51] Branda and coworkers reported the lowest coupling yields of 4% during the synthesis of DTE derivatives having a bulky 2,5-dimethylthienyl groups at the reactive positions (Table 1.2, entry 4).[46,50]

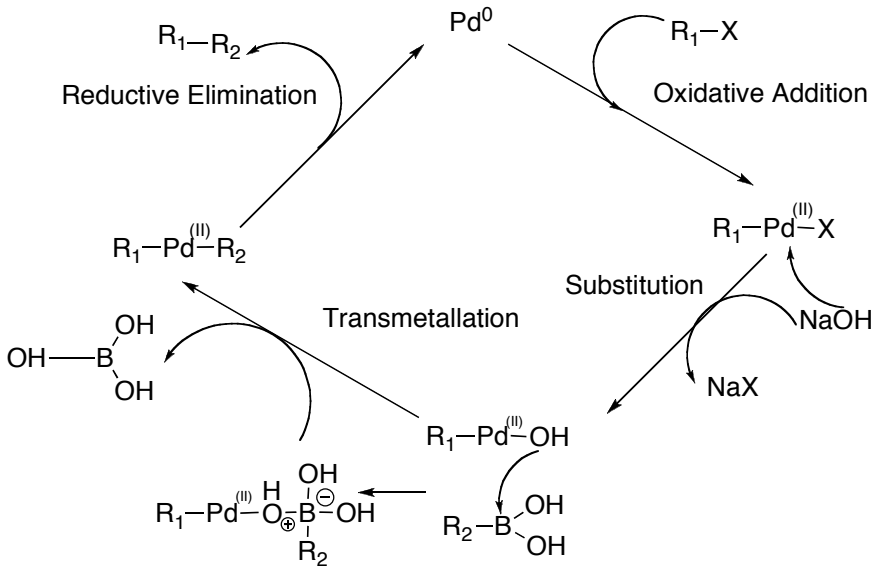
Table 1.2 Effects of bulky substituents on coupling reactions of DTEs.



Entry	R1	R2	% Yield
1			45
2			17
3			44
4			4

1.6 Suzuki–Miyaura cross-coupling reaction

One of the most frequently used C–C bond formation reactions in organic synthesis is the Suzuki–Miyaura cross-coupling reaction. This is commonly referred to as the Suzuki coupling. In our synthesis, the Suzuki coupling has been employed to couple aryl substituents to the substituted thiophenes. This coupling involves an organic reaction of an organoboron compound such as an aryl- or vinyl-boronic acid with an organic halide in the presence of a base and a palladium catalyst.[52] The reaction mechanism proceeds by an oxidative addition of palladium(0) to the halide to form an organo-palladium (R_1-Pd(II)-X) complex (Scheme 1.4). The halide is displaced from the complex to form a more reactive organopalladium alkoxide (R_1-Pd(II)-OR_3) complex.



Scheme 1.4 The proposed mechanism for the Suzuki–Miyaura cross-coupling reaction (Adapted from reference 52).

The (R_1-Pd(II)-OR_3) complex undergoes transmetallation with the aryl boronic acid which places the two aryl groups on the same palladium center to form another organoborane species (R_1-Pd(II)-R_2). Reductive elimination of the organoborane yields the coupled product and the original palladium catalyst is regenerated.

1.7 Photoresponsive DTE-based amphiphilic systems

Recently, there has been considerable efforts towards the design and synthesis of photoresponsive self-assembling structures for their potential application in areas such as drug delivery, ion transport, and biological imaging.[53-60] Reversible photoresponsive self-assemblies are desirable because light is used as the only input stimulus. Photoresponsive self-assemblies are generally prepared by incorporating amphiphilic photochromic molecules into lipid vesicles or micelles. These amphiphiles contain hydrophobic and hydrophilic components. DTEs have been shown to be the most promising candidates for such applications when compared with other photochromic systems due to their superior photochromic properties.[1,9]

Several amphiphilic diarylethenes have been reported so far.[56-60] For example, Feringa and coworkers prepared an amphiphilic DTE **m** (Figure 1.8) that contains a hydrophobic cholesterol unit and ethylene glycol side chains with a hydrophilic pyridinium group.[58] An aqueous solution of this DTE was shown to reversibly form vesicles from a planar bilayer following UV light. The change in the aggregation behavior of the closed-ring isomer was thought to arise from the cumulative effects of both cholesterol/ethylene glycol side chains and the methyl groups at the reactive carbons. The side chains are forced into specific orientation in the closed-ring form while

the methyl groups are oriented out of the plane. This arrangement interferes more with the packing of the DTE and provides the right circumstances to form vesicles.

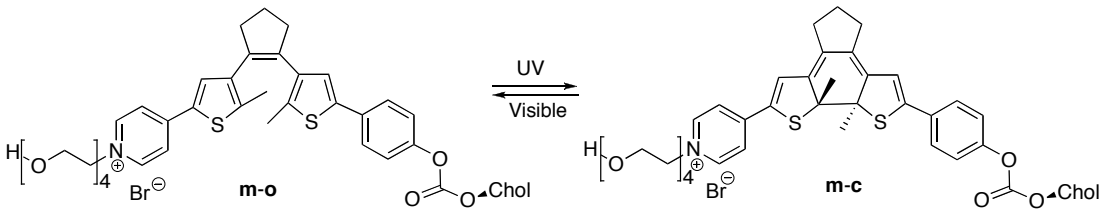


Figure 1.8 Reversible photochromic reactions of **m**, Chol: cholesterol; **m-o**: open-ring isomer; **m-c**: closed-ring isomer (Adapted from reference 58).

In another study, Zhou and coworkers reported on an amphiphilic DTE derivative **n** with histamines as side chains and investigated its light-triggered self-assembling behavior (Figure 1.9).[59] Irradiation of the solution with UV light led to a change in morphology from a nanofiber to a nanosphere. It was observed that the radius of the self-assembled nanosphere was pH dependent (i.e., the radius was greater under low pH conditions). This was associated with the weakening intermolecular strength as the protonated histamines lose the two protons at high pH ranges. Another research group also synthesized an amphiphilic DTE **o** that possessed hydrophilic and hydrophobic parts at the two ends of the rigid DTE core (Figure 1.9).[60] The compound formed stable vesicles in aqueous solution and displayed switchable fluorescence.[59] The fluorescent vesicle was observed to enter living cells with low cytotoxicity and switchable fluorescence was achieved in the cells upon alternate irradiation with UV and visible light.

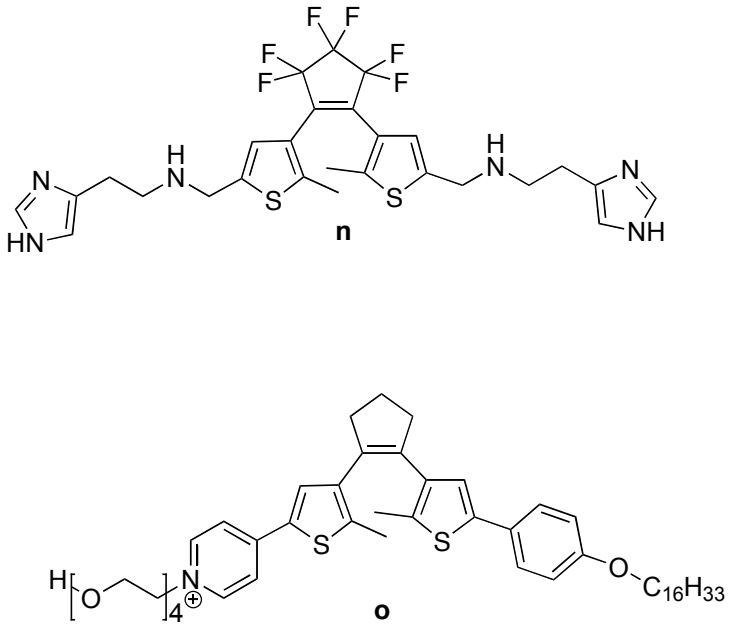


Figure 1.9 Chemical structures of the open-ring isomers of **n** and **o**.

In a recent report from our group, a series of asymmetrical amphiphilic DTEs **p**, **q**, and **r** were synthesized (Figure 1.10).[16] These DTEs were designed to include a charged quaternary ammonium substituent at the end of an alkyl chain to mimic the structure of a surfactant and to improve their organization in lipid vesicles. As shown, DTEs **p** and **q** integrated bulky phenylethynyl substituents at the reactive carbons. A DTE with phenylethynyl substituents at the reactive carbons has been previously shown to undergo a large change in molecular geometry upon photoisomerization.[61] This large change in the molecular structures may be beneficial in causing significant disruption of the lipid bilayer membrane. The DTEs were included in lipid vesicles and the effect of their inclusion on proton permeation was studied. An apparent substituent effect was observed as the methyl-substituted DTE showed lower rates of proton permeability than

the bulkier phenylethynyl-substituted DTE derivatives.

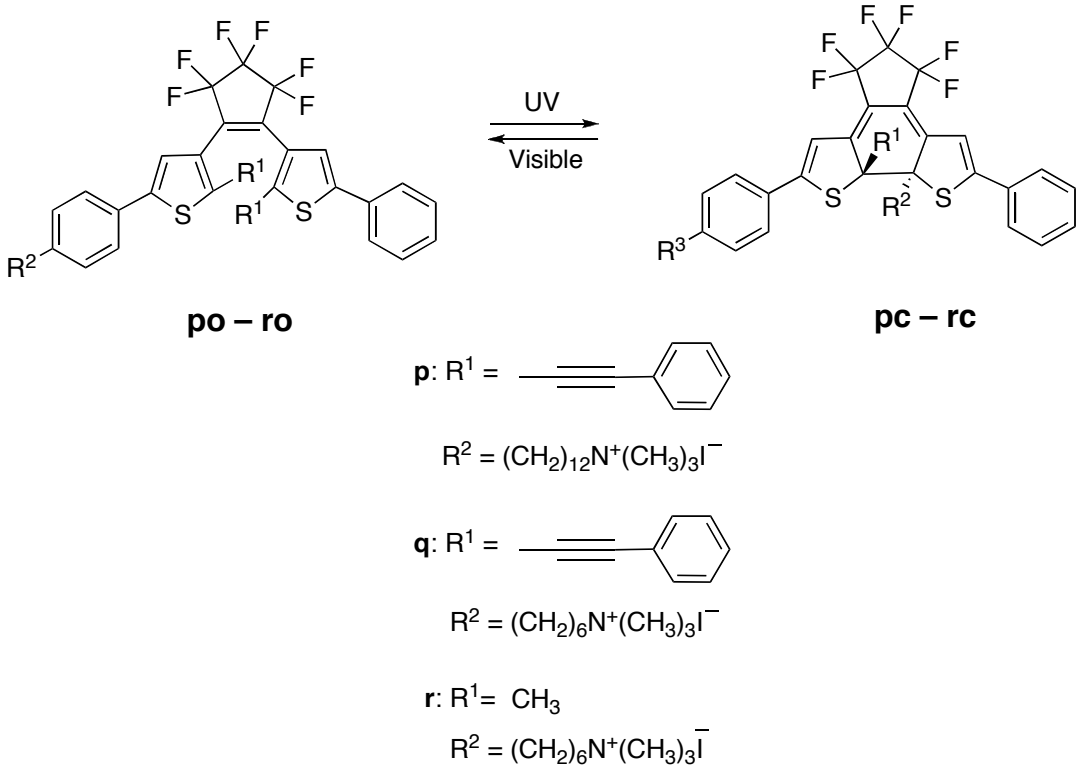
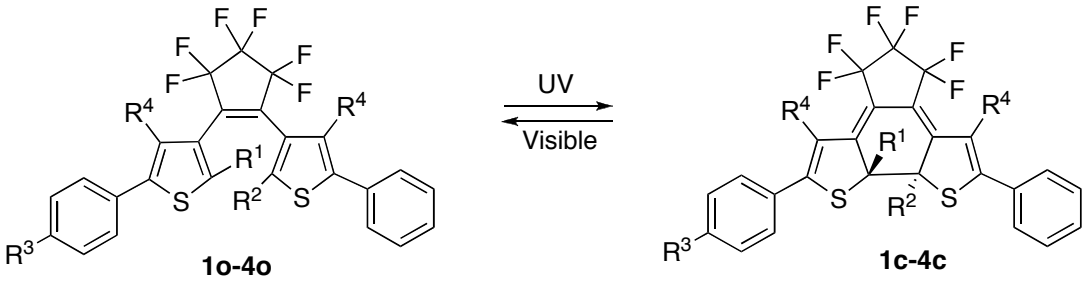


Figure 1.10 Structures of amphiphilic DTEs **p**–**r** (Adapted from reference 16).

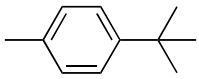
1.8. Research objectives

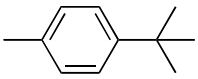
The main objective of this work is to design the syntheses of asymmetrical DTEs **1**–**4** (Scheme 1.5) that adhere to the following design principles:

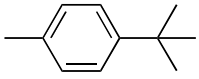
1. A terminally charged alkyl ammonium substituent at the periphery of the thiophene. This is incorporated to improve the amphiphilicity of the DTEs.
2. Methyl substitution at the 4– and 4'–positions of the thiophene rings. This is expected to enhance fatigue resistance of the DTEs.
3. *t*-Butylphenyl substituents at the 2– and 2'–position of the thiophene rings. This is expected to enhance photocyclization quantum yield and ensure a large change in molecular geometry upon photoisomerization.



1: $R^1 = R^2 = CH_3$; $R^3 = (CH_2)_6N^+(CH_3)_3I^-$; $R^4 = CH_3$

2: $R^1 = R^2 =$  ; $R^3 = (CH_2)_6N^+(CH_3)_3I^-$; $R^4 = CH_3$

3: $R^1 = CH_3$; $R^2 =$  ; $R^3 = (CH_2)_6N^+(CH_3)_3I^-R^4 = CH_3$

4: $R^1 = R^2 =$  ; $R^3 = (CH_2)_6N^+(CH_3)_3I^-$; $R^4 = H$

Scheme 1.5 Reversible photoisomerization of DTEs **1**–**4**, where **1o**–**4o** and **1c**–**4c** are the open-ring and closed-ring isomers, respectively.

2.0 Results and Discussion

In this section, the syntheses of asymmetrical amphiphilic DTE derivatives **1**–**4** are presented in order. These DTEs were prepared for their potential use as photoresponsive membrane disruptors in lipid vesicles. For this reason, all DTEs were designed to include characteristics of amphiphiles. Specifically, a charged quaternary ammonium substituent was introduced at the end of the alkyl chain on the periphery of one thiophene while a neutral hydrophobic group was attached to the 3–position of the thiophene ring system. It is also important that the DTEs possess high fatigue resistance so that the reversible photoisomerization can be repeated many times without a significant degradation. Therefore, DTEs **1**–**3** were designed to include methyl substituents at the 4– and 4'–positions as this structural feature has been shown to enhance the fatigue resistance by suppressing a well-known rearrangement of the closed-ring isomer to form an irreversible photoproduct.[22-25] In addition, DTEs **2–4** were designed to include bulky *t*-butylphenyl substituents at the 2– and 2'–positions of the thiophene rings. The presence of bulky substituents at the reactive carbons is known to favour the antiparallel conformation of the DTE open-ring isomer, which often leads to an increase in the photocyclization quantum yield.[31] Furthermore, DTEs with bulky substituents undergo large changes in molecular geometry upon cyclization. As a result, these DTEs may have utility as photoresponsive membrane disruptors.

The syntheses of these DTEs was achieved by modifying previously reported procedures.[62] Most of the starting materials (i.e., thiophene derivatives) were different from those of previous work. The synthetic routes used to prepare compounds **1**–**4** are outlined in sections 2.2–2.5. Our synthetic methodology commonly includes two

important coupling reactions. The first reaction is the regioselective substitution at the 2– and 5–position of thiophene derivatives with aryl- and alkylaryl-substituted boronic acids via Suzuki coupling. In most cases, these substitution reactions were successful resulting in moderate yields (45–60%). Secondly, lithium-halogen exchange reactions were used to generate the 3-thienyllithium intermediates that were then coupled to mono-substituted perfluorocyclopentene derivatives via a nucleophilic addition–elimination reaction. The efficiency of these coupling reactions was greatly influenced by the nature of the substituents at the 2–, 2–', 4–, 4–' and 5–, 5'–positions of the thiophene ring systems.

2.1. Synthesis of the boronic acid

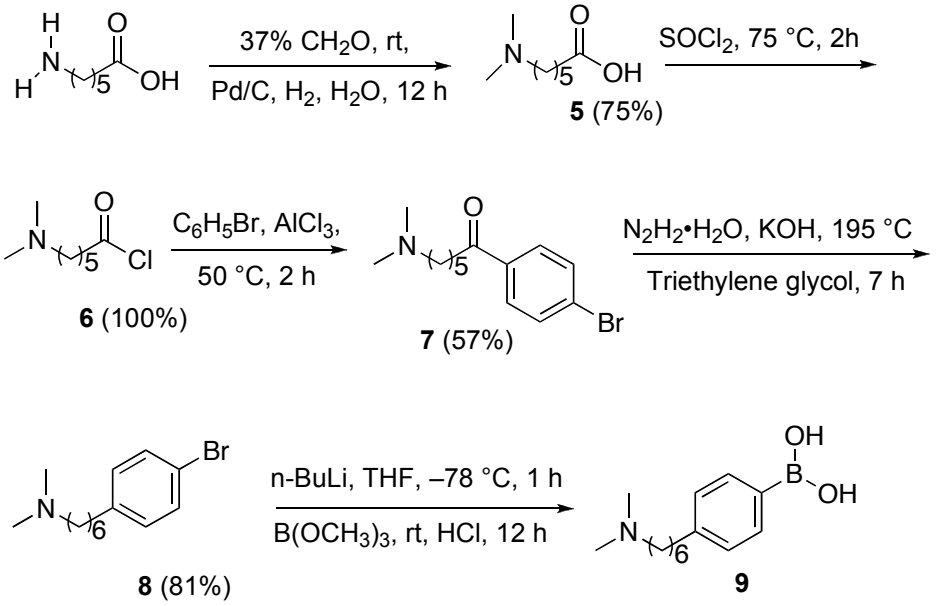
The first objective of this work was to prepare asymmetrical DTEs that exhibit amphiphilic characteristics. This was achieved by incorporating a long alkyl chain fragment terminated by a cationic ammonium substituent at the periphery of the thiophene ring. For this reason, the synthesis of 4-(6-(*N,N*-dimethylamino)hexyl)phenylboronic acid (**9**) was a vital part of this work. A commercially available 6-aminohexanoic acid is used as the starting material. This tertiary amine served as the precursor to the cationic ammonium substituent in our target DTEs. The synthetic methodology for **9** (Scheme 2.1) began with a reductive amination of 6-aminohexanoic acid using 37% formaldehyde and hydrogen gas in the presence of palladium on carbon, as a catalyst.[62] This produced the 6-(*N,N*-dimethylamino)hexanoic acid (**5**) in high yield (75%). The high yield observed may be attributed to the good solubility of the amino acid in water. 6-Aminohexanoic acid is polar and therefore,

readily soluble in water which was used as the solvent in this reaction.

Although palladium-catalyzed reductive amination is a high yielding transformation and minimizes unwanted side reactions, palladium on carbon is expensive to use as it was not used in catalytic amounts. This prompted the exploration of other transition metal-free methods to synthesize **5**. One such method involved the modification of the well-known Eschweiler–Clark reaction.[63] Here, 37 % formaldehyde in the presence of triethylamine was employed as the reducing agent, as well as the methylating agent, and toluene was used as a solvent. Under high temperatures (i.e., 130 °C), formaldehyde is converted to a hydrated methanediol. In the presence of a base, methanediol is converted into formic acid via a proton transfer reaction, creating a favourable precursor for the Eshweiler-Clark reaction to proceed. Although methylation of the amine was achieved, the product was recovered as a protonated tertiary amine. However, the presence of the charge was not problematic since the next step of our scheme is carried out under acidic conditions. Despite the lower yield (40%) when compared with the Pd-catalyzed reaction, this method is simple and cost-effective. With improved work-up procedures, the yield of this reaction can be increased.

The carboxylic acid **5** was then reacted with thionyl chloride to produce an acyl chloride 6-(*N,N*-dimethylamino)hexanoyl chloride (**6**). Thionyl chloride acts as both the reactant and the solvent in this reaction. There was no purification necessary for this reaction because the by-products are both gaseous. Any excess thionyl chloride was removed by vacuum distillation. Without further purification, the acyl chloride **6** was used in a Friedel–Crafts acylation reaction with bromobenzene in the presence of aluminum chloride to produce 1-(4-bromophenyl)-6-(*N,N*-dimethylamino)hexan-1-one

(**7**) in moderate yield (57%).



Scheme 2.1 The synthesis of boronic acid **9**.

Isolation of compounds with terminal amines is difficult especially under acidic conditions. This is because the ammonium salt has limited solubility in organic solvents. In such cases, an acid-base extraction is necessary to improve the solubility of **7** in dichloromethane and enhance its isolation. This was achieved by adding a 2 M aqueous solution of sodium hydroxide to adjust the pH of the mixture to above 12 before extraction. Additionally, for aluminum chloride catalyzed reactions, aluminum chloride will hydrolyze in aqueous solution to form partially-hydrated aluminum hydroxide salts, which reduces extraction efficiency. The salts are amphoteric and will dissolve under strongly acid and strongly basic conditions. Therefore, by converting to more basic conditions, efficient extraction of the products to the organic phase could be achieved.

Compound **7** also has a very low R_f value and tailing was commonly observed on the silica gel. This was encountered because a silica gel column is mildly acidic and **7** can become protonated as it moves through the stationary phase. As a result, triethylamine was added to the mobile phase to help reduce interactions between **7** and these acidic sites on silica gel. A reduction in tailing was observed following the addition of triethylamine.

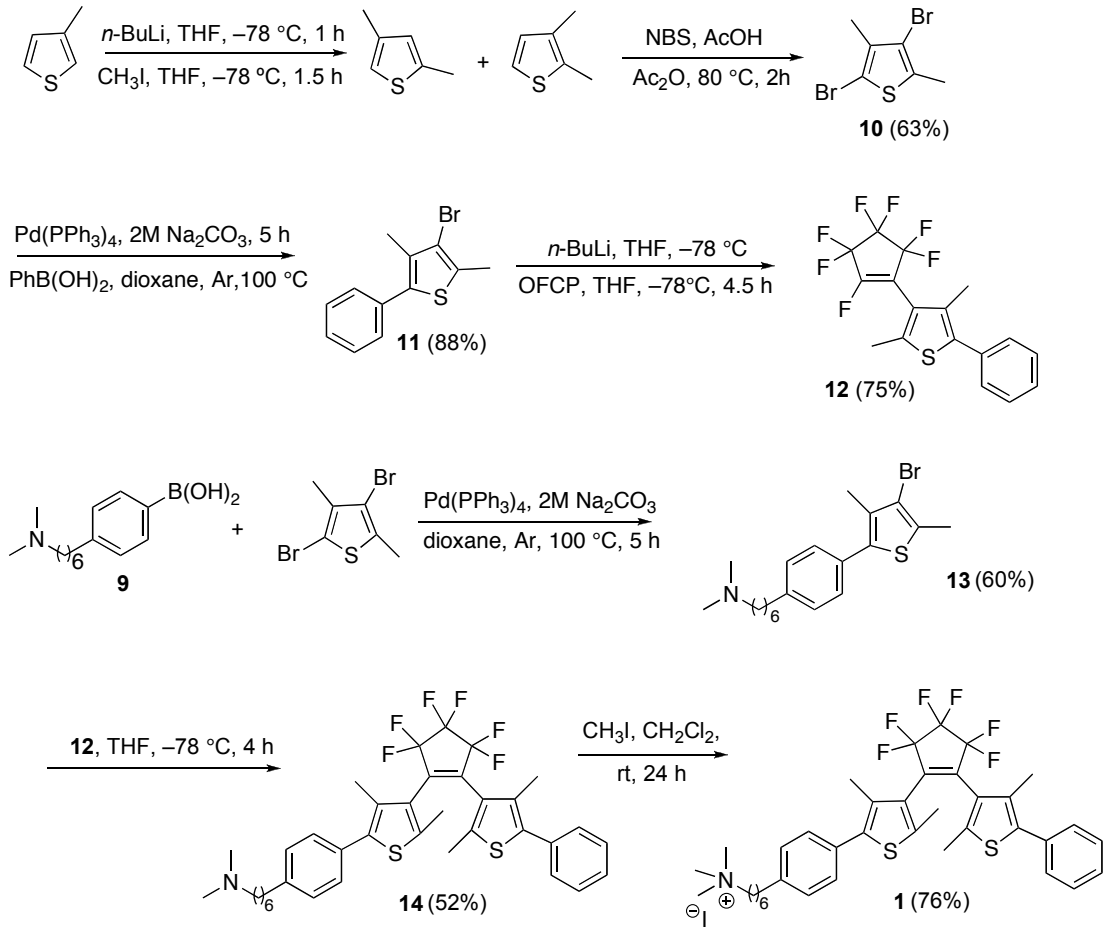
A Wolff-Kishner reduction of **7** was carried out in triethylene glycol solvent under high temperature (i.e., 195 °C) to give 6-(4-bromophenyl)-*N,N*-dimethyhexan-1-amine (**8**). The reaction mechanism is proposed to proceed via a condensation of the carbonyl-containing compound with hydrazine to form a hydrazone intermediate. Compound **8** was then converted to its corresponding aryl boronic acid **9**. Several methods have been reported to prepare boronic acids; however, the most common and affordable method involves a lithium-halogen exchange with aryl halides followed by an electrophilic trapping with trimethoxyborane.[42] In this method, the aryl halide **8** is converted to a nucleophilic lithium salt, which is then reacted at low temperatures with trimethoxyborane to form a boronic ester. Acid hydrolysis of the boronic ester gave the desired boronic acid. At neutral pH, compound **9** is zwitterionic, which makes extraction into ethyl acetate difficult. Therefore, the pH of the reaction mixture was adjusted to nine with the addition of a saturated aqueous solution of sodium hydrogen carbonate prior to extraction. Again, this pH adjustment ensures the terminal amine is unprotonated improving the extraction efficiency. This alkylboronic acid was used as a precursor for the Suzuki coupling reactions with substituted thiophenes.

2.2 Synthesis of 1

The second objective of this work was to design asymmetrical amphiphilic DTEs that incorporate methyl substituents at the 4– and 4'–positions of the thiophene rings. As discussed earlier, DTEs substituted at the 4– and 4'–positions have been shown to display high fatigue resistance, thus DTE **1** was designed to possess this structural feature. The synthetic route for the preparation of **1** is shown in Scheme 2.2. The precursor, 2,4-dibromo-3,5-dimethylthiophene, was prepared in two steps from a commercially available 3-methylthiophene, following literature procedures.[35] Methylation of 3-methylthiophene is possible at both the C2 and C5 positions. Electrophilic aromatic substitution is preferred at these positions than the C4 position. This is because the intermediates produced are more stable by resonance than a possible intermediate involving the C4 position. As a result, the reaction of 3-methylthiophene with *n*-BuLi and iodomethane gave a yellow, oily mixture of 2,4-dimethylthiophene and 2,3-dimethylthiophene in a ratio of 1:1.

Notably, these compounds have similar retention factor (R_f) values when spotted on a silica gel thin-layer chromatography (TLC) plate. Therefore, a fractional distillation was attempted to isolate 2,4-dimethylthiophene from the mixture. However, only a partial separation was possible as the boiling point ranges of these derivatives overlap (i.e., 139–141 °C and 140–141 °C for 2,4-dimethylthiophene and 2,3-dimethylthiophene, respectively).[71] As a result, the mixture was used in the next step without further purification. Fortunately, the target, 2,4-dibromo-3,5-dimethylthiophene (**10**), and side product, 2,3-dibromo-4,5-dimethylthiophene, are easily distinguishable by TLC due to their differences in molecular polarity. The relative position of the bromine atoms in the

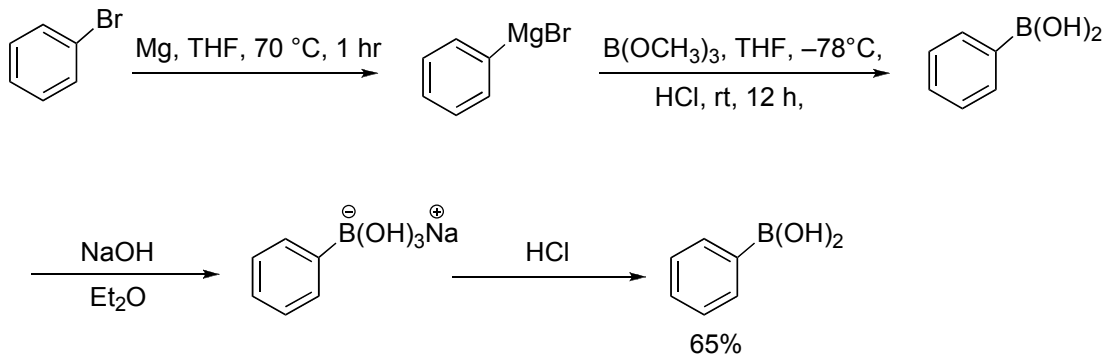
target leads to a reduction in molecular polarity when compared to the side product, which has a larger molecular dipole moment. As a result, it was possible to isolate **10** (63% yield) from the side product after bromination.



Scheme 2.2 Synthesis of **1**.

3-Bromo-2,4-dimethyl-5-phenylthiophene (**11**) was prepared in an excellent yield (88%), from a Suzuki coupling of **10** and phenylboronic acid. Although commercially available, phenylboronic acid was synthesized by an electrophilic borylation of phenylmagnesium bromide. This method was chosen as the reagents were easily

available.[66] Phenylmagnesium bromide was prepared separately from bromobenzene and magnesium metal (Scheme 2.3). We also purified phenylboronic acid using a method reported by Basu and coworkers, which involves a conversion of boronic acids into sodium alkyl trihydroxyboronate salts.[44] The salt was prepared by treating phenylboronic acid in diethyl ether with a saturated aqueous solution of sodium hydroxide. This leads to the quaternization of boron, which precipitates as a sodium salt of the phenylborate. After an acid-base extraction and recrystallization from methanol, phenylboronic acid was obtained as a crystalline solid in moderate yield (65%).



Scheme 2.3 Preparation of phenylboronic acid.

Compound **11** was lithiated and successfully coupled with OFCP via an addition–elimination reaction to yield 3-(2,3,3,4,4,5,5-heptafluorocyclopent-1-enyl)-2,4-dimethyl-5-phenylthiophene (**12**) in a fairly good yield (75%). The order of addition of the two reagents (OFCP and **11**) plays an important role in this step. To maximize the formation of the mono-substituted product over the di-substituted side product, the lithium salt was added dropwise (i.e., 1 drop/20 sec) to a diluted solution of OFCP in THF at low temperature. Commonly, the major side product recovered from this reaction was the

debrominated starting material. Although every attempt was made to remove moisture from our reaction set-up, we suspect that the 3-thienyllithium formed was reacting with trace amounts of water, given that organolithium intermediates are strong bases and reactive towards micromolar concentrations of water. For example, 1.04 μL of water would result in 10% yield of the debrominated product under the concentration conditions used in this reaction.

The peripheral side chain 6-(4-(4-bromo-2,5-dimethylthiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine (**13**) is required to achieve asymmetry in **1**. Suzuki coupling of **9** and **10**, followed by recrystallization from methanol gave **13** as a light yellow solid in a good yield (60%). Cross-coupling reactions are known to occur preferentially at the C2 position rather than the C3 due to a better stability of the intermediate thus **13** was the major product. The ^{1}H NMR spectra for **13** and **8** the precursor to **9** is shown in Figure 2.1. There are two additional peaks in the spectrum of **13** when compared with the spectrum of **8** (i.e., †1 and †2 at 2.25 and 2.42 ppm, respectively). We assigned these peaks to the two methyl groups on thiophene, which provides support for a successful coupling reaction.

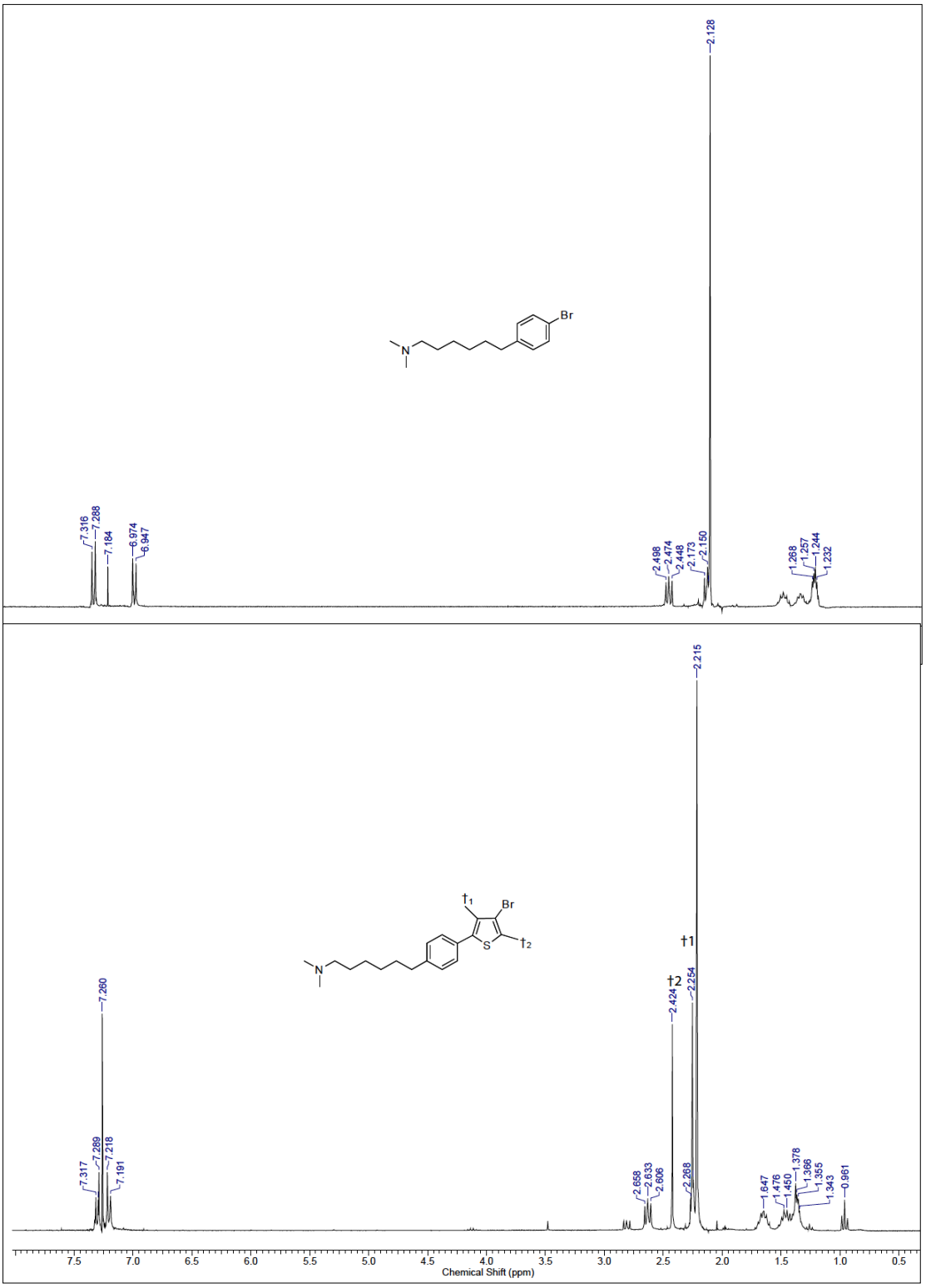


Figure 2.1 A comparison of ^{1}H NMR spectra for **8** (top) and **13** (bottom). The †1 and †2 represent the methyl protons on thiophene.

One of the side products recovered from this coupling reaction was a protodeboronated 6-(phenyl)-*N,N*-dimethylhex-1-amine (**s**) shown in Figure 2.2a. Boronic acids are known to suffer from base-catalyzed protodeboronation under Suzuki coupling conditions.[67,68] This reaction arises from a pre-equilibrium between boronic acid and the hydroxide ion to form a boronate intermediate, which subsequently reacts with water (Figure 2.2b). To minimize the occurrence of this pathway, various methods have been investigated.[68] For example; boronic acids can be converted to *N*-methyliminodiacetic acid boronates, aryltrifluoroborates, or trihydroxyboronate salts.[68] These alternative methods help to ensure a slow, in situ release of the boronic acid (i.e., a low concentration), which minimizes protodeboronation. As discussed earlier, we successfully purified phenylboronic acid by converting it to the respective trihydroxyboronate salt. However, we chose not to test this method with larger boronic acid derivatives at this time.

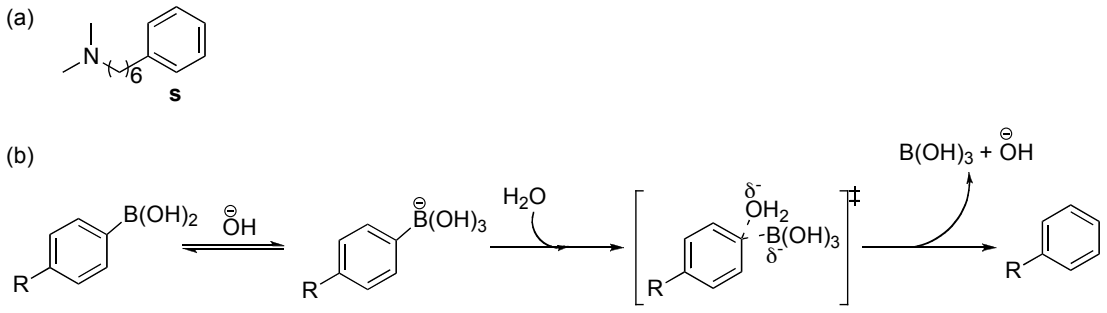


Figure 2.2 (a) Structure of the protodeboronated compound (**s**). (b) Base-catalyzed protodeboronation of a boronic acid (Adapted from reference 68).

To enhance the yield of **13**, we attempted to convert **10** to a boronic acid instead of converting **8** to the respective boronic acid. The main challenge encountered in this approach is that it produced a mixture of boronic acids. The lithium-halogen exchange reaction was not regioselective towards the 2–position of thiophene. Therefore, **13** was lithiated and coupled with **12** to produce the DTE precursor **14** as a white solid in moderate yield (52%). Gravity column chromatography was necessary to isolate **14** from the side products. The yield in this coupling reaction was comparable to that of an earlier methylated DTE reported by Irie and coworkers.[1]

Finally, conversion of the tertiary amine to a quaternary amine with methyl iodide, and recrystallization from diethyl ether gave **1** in a high yield (76%). A comparison of the ^{1}H NMR spectra of **14** and **1** reveals a distinct change accompanying the methylation step. The alkyl regions of the two spectra from 1.0 to 6.0 ppm are shown in Figure 2.3. Significant differences are observed for the methyl protons attached to the nitrogen atom and the methylene protons neighboring the nitrogen atom labeled †1 and †2 in Figure 2.3. The methyl protons of **14** appear as a sharp singlet at 2.21 ppm while the methylene protons appeared as a triplet at 2.25 ppm. However, in the charged DTE, both the methyl and methylene protons are shifted downfield to 3.42 ppm and 3.52 ppm, respectively. This shift reflects the change in electron density from a neutral tertiary amine to a quaternary ammonium salt. The cationic nitrogen withdraws electron density from the neighbouring atoms. This renders the local magnetic field around the nuclei less effective at canceling out the external magnetic field, resulting in higher signal frequency and thus, larger chemical shift.[71] Based on this NMR supporting evidence, DTE **1** was isolated.

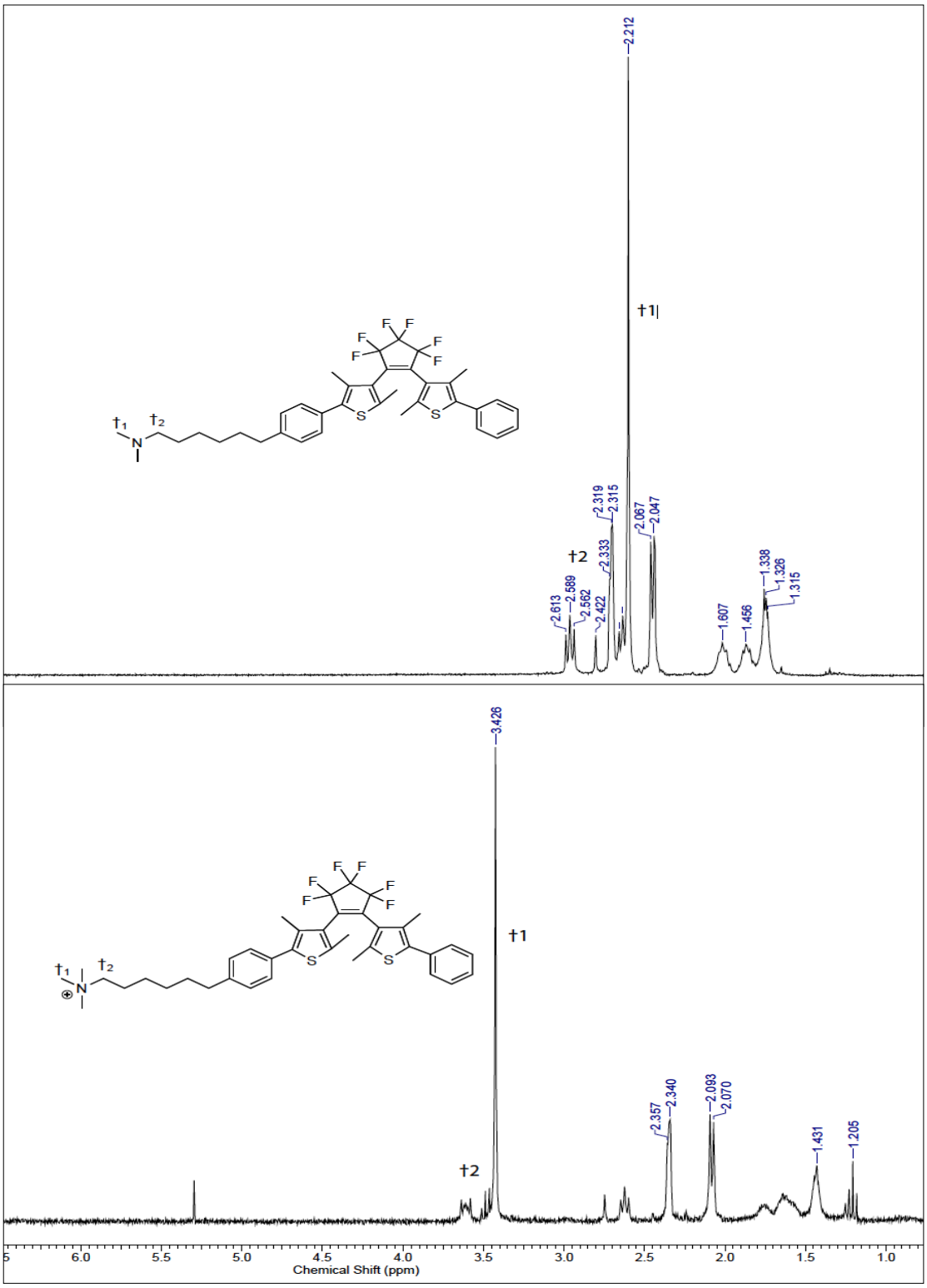


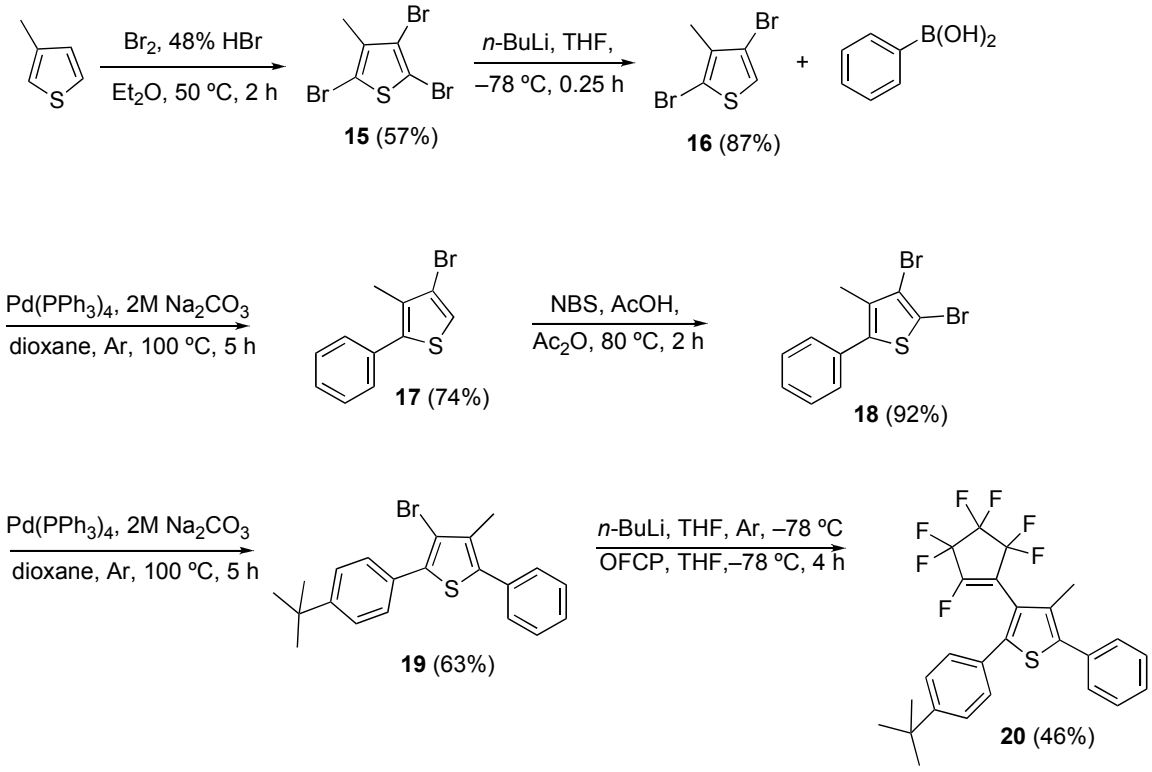
Figure 2.3 A comparison of ^{1}H NMR spectra of the neutral DTE (top) and the charged DTE (bottom) in $CDCl_3$.

2.3 Synthesis of 2

The third objective of this work was to synthesize a DTE that incorporates bulky *t*-butylphenyl substituents at the 2– and 2'–positions of the thiophene rings. DTEs with bulky substituents at the reactive carbons have been reported to display enhanced photocyclization quantum yields.[1,28] This is because bulky substituents at the reactive carbons favour the photoactive antiparallel conformation of the open-ring isomer. Furthermore, DTEs with bulky substituents undergo large changes in molecular geometry upon photoisomerization, which can cause membrane disruption in lipid vesicles.[16] The second target compound, 6-(4-(4-(2-(2-(4-*t*-butylphenyl)-4-methyl-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl)-3,5-dimethylthiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-ammonium iodide (**2**), was proposed to achieve this goal. Similar to **1**, the inclusion of methyl substituents at the 4– and 4'–positions was also desired.

3-Methylthiophene also served as the starting material for the synthesis of **2** (Scheme 2.4). The synthesis began with a complete bromination of 3-methylthiophene to produce 2,4,5-tribromo-4-methylthiophene (**15**) in moderate yield (57%). The resulting compound was then regioselectively debrominated at the 2–position using *n*-BuLi to give 2,4-dibromo-3-methylthiophene (**16**) in an excellent yield (87%). The regioselective debromination step takes advantage of the electron-withdrawing bromine atom at the 3–-position, which stabilizes the carbanion intermediate at the 2–position when compared with the electron-donating methyl group at the 5–position. Nonetheless, 2,3-dibromo-4-methylthiophene was formed as a side product in some 10% yield. Although the R_f value of this side product is close to that of **16** (i.e., 0.78 and 0.80, respectively, the separation of these two compounds should be relatively straightforward due to this difference in

polarity. As anticipated, isolation of **16** was achieved by using a long silica gel column and elution by gravity. Suzuki coupling conditions were then applied to couple phenylboronic acid with **16** to give 3-bromo-4-methyl-5-phenylthiophene (**17**) in a high yield (74%).



Scheme 2.4 Synthesis of **20**.

A comparison of ^{1}H NMR spectra for **16** and **17** shows regioselectivity towards the C2 position (Figure 2.4). A distinct singlet was observed at 7.22 ppm for **16**, which was assigned to the C5 proton on the thiophene ring (Figure 2.4, top). After Suzuki coupling, the peak assigned to C5 shifted downfield and a new multiplet observed in the aromatic region. The multiplet integrated to five protons, which matches the number of aromatic

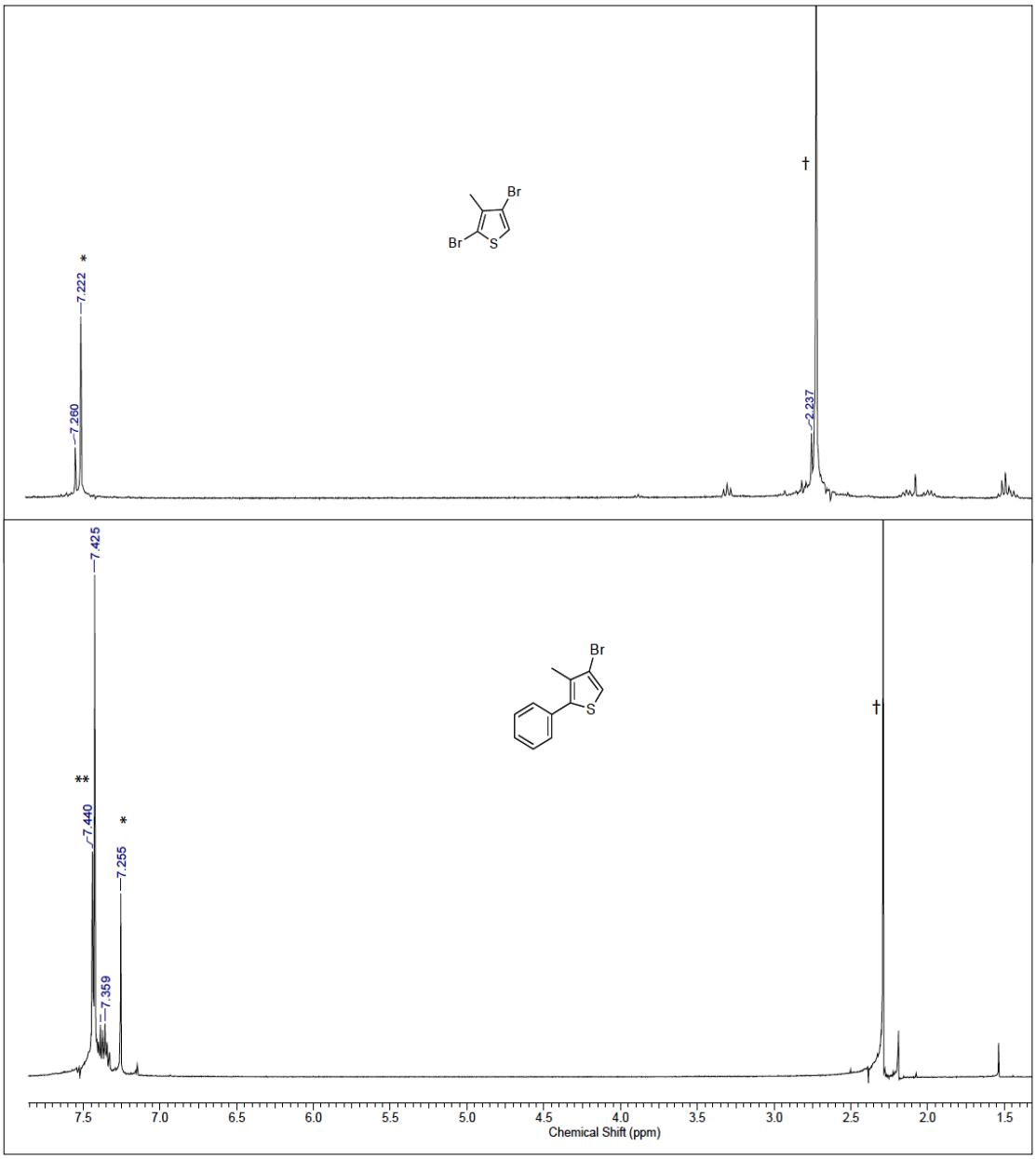


Figure 2.4 A comparison of ^{1}H NMR spectra of 16 (top) and 17 (bottom) showing regioselective substitution. The peaks labeled represent the following proton environments: * thiophene; ** 2-phenyl ring; † methyl protons.

protons on the phenyl ring.

Compound **17** was brominated with *N*-bromosuccinimide (NBS) in presence of glacial acetic acid to give 2,3-dibromo-4-methyl-5-phenylthiophene (**18**) in excellent yield (92%). This bromination is thought to proceed by a multistep electrophilic aromatic substitution mechanism. In the first step, a nucleophilic attack on the electrophilic bromine produces a high-energy carbocation intermediate often referred to as a sigma (σ) complex. Acetic acid was necessary to stabilize the σ complex in this reaction as well as polarize the NBS. In the second step, a proton is removed from the σ complex to generate the product and succinimide as a by-product. Succinimide is soluble in water, so it was easily removed during the extraction process. As expected, the ^{1}H NMR spectrum of **18** shows no singlet at 7.22 ppm, which was associated with the C5 proton of **17** (Figure 2.5). Compound **18** then underwent Suzuki coupling with *t*-butylphenyl boronic acid to give 3-bromo-2-(4-*t*-butylphenyl)-4-methyl-5-phenythiophene (**19**) in moderate yield (63%). There are some distinct differences in the ^{1}HNMR spectra of **18** and **19** shown in Figure 2.5. The spectrum of **19** shows an additional sharp singlet peak at 1.38 ppm and unresolved multiplets with a doublet at around 7.64 ppm. The former peaks were assigned to the nine chemically equivalent *t*-butyl protons while the later were assigned to the phenyl protons. This analysis provides support for a successful Suzuki coupling between **18** and the *t*-butylphenyl boronic acid to give **19**.

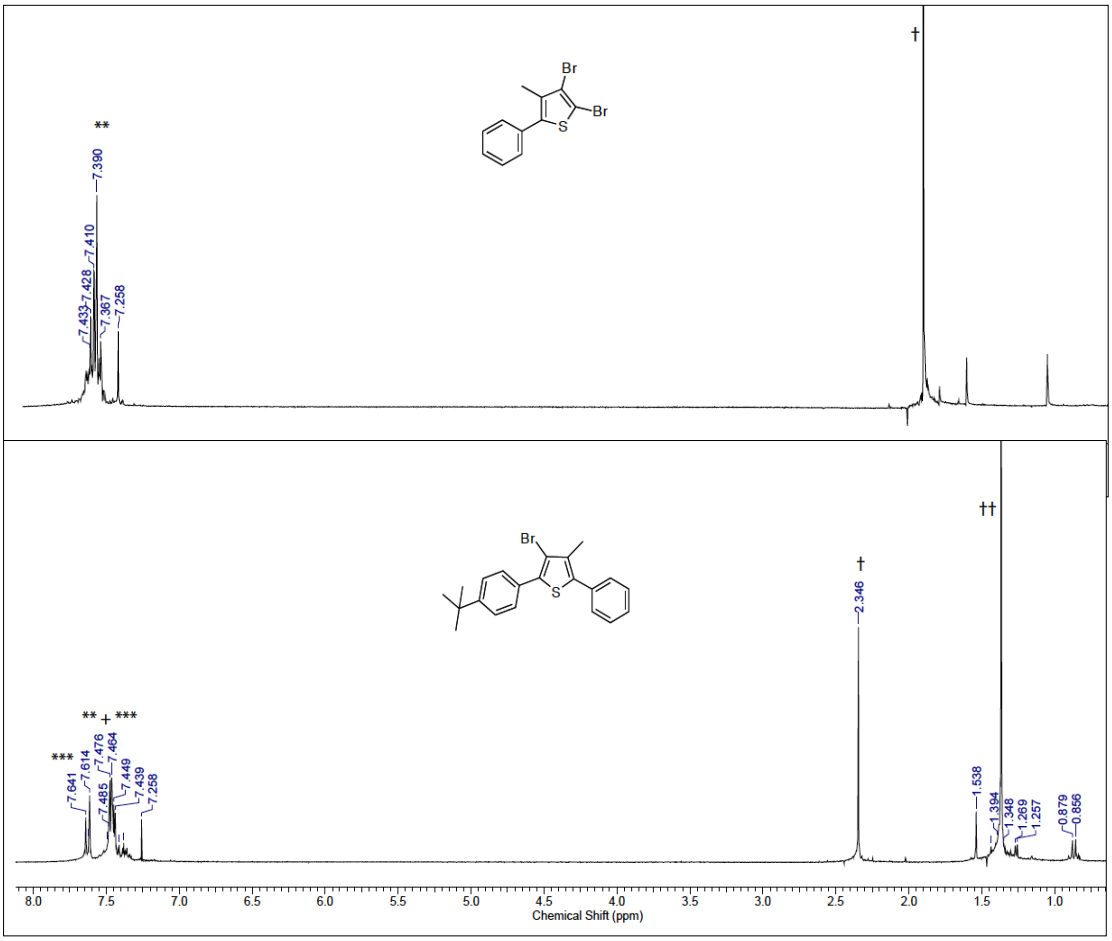


Figure 2.5 ^{1}H NMR spectra of **18** and **19** showing regioselective substitution at C2. The peaks from the different proton environments are labeled as follows: ** phenyl ring; *** *t*-butylphenyl ring; † methyl protons on thiophene; †† *t*-butyl protons.

After lithiation of **19**, the corresponding 3-thienyllithium intermediate was treated with OFCP to obtain **20** in moderate yield (46%). Although the syntheses of both **20** and **12** proceed in a similar manner, the percent yield of **20** was significantly lower than that of **12** (75%). This lowering of yield could be attributed to a steric effect caused by the presence of the *t*-butylphenyl substituent on **20**. The ^{1}H NMR spectrum of **20** showed a sharp singlet at 1.34 ppm that integrated to nine protons from the *t*-butyl protons and another singlet at 2.20 ppm from the methyl protons attached to the thiophene ring. In the aromatic region, not all the signals appeared as well-resolved doublets. In addition, there were four characteristic multiplet signals in the ^{19}F NMR spectrum (Figure 2.6, top; –130.4, –125.5, –119.6, –109.1 ppm). These signals correspond to the four inequivalent fluorine regions of the cyclopentene ring. The ^{13}C NMR spectrum (Figure 2.6, bottom) showed a total of 14 peaks with some overlapping peaks in the aromatic region. Interestingly, one sp^3 carbon atoms in the perfluorocyclopentene ring could not be assigned. As shown in the spectra, the intensity of the peaks corresponding to the carbon atoms attached to fluorine atoms are significantly reduced compared to the protonated carbons. This may be a result of lack of a full Nuclear Overhauser enhancement (NOE) in the fluorinated carbons. Also, due to the high abundance of ^{19}F, carbon-fluorine (C–F) coupling is a common feature observed in ^{13}C NMR spectra of perfluorinated compounds.[70] In this case, we would expect to see a C–F splitting on the resonance peaks from the carbon atoms bonded to fluorine in the perfluorinated cyclopentene ring (i.e., †1 and †2, Figure 2.6). This coupling phenomenon would have been clearly observed in the ^{13}C spectra had we increased the number of scans.

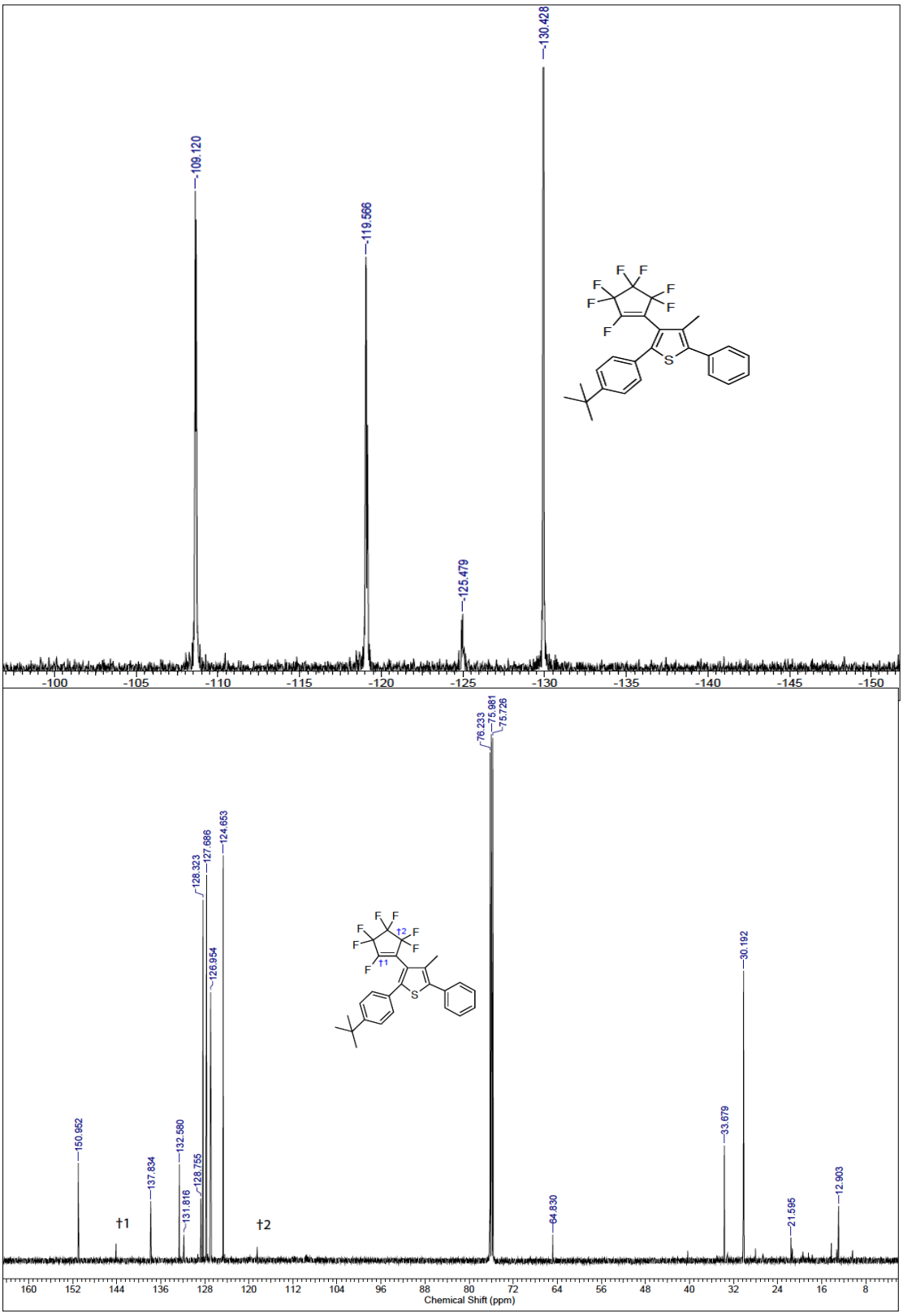
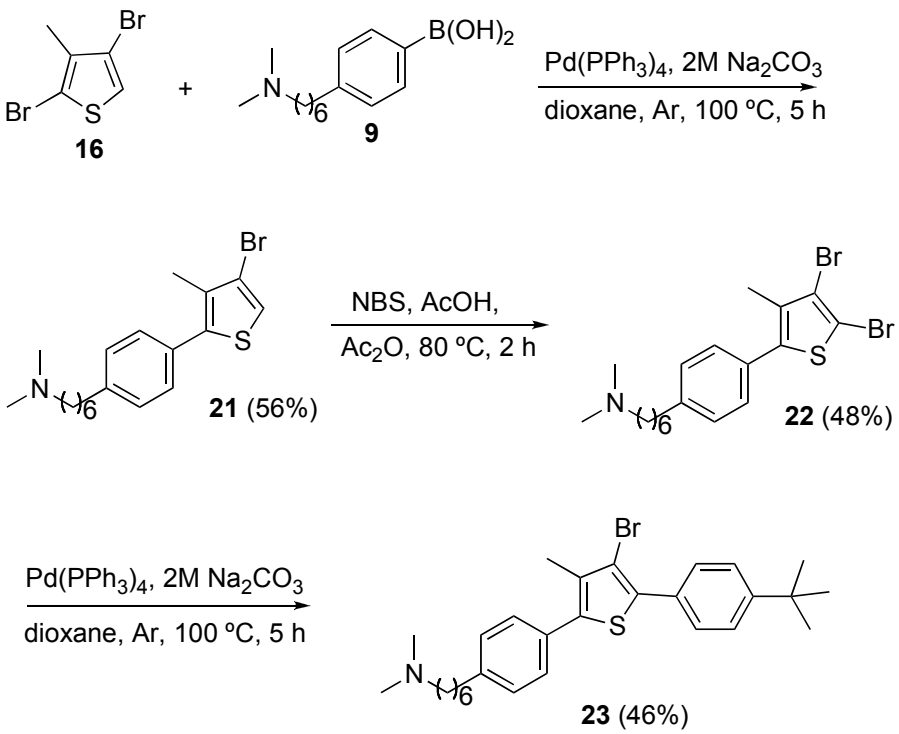


Figure 2.6 A comparison of ^{19}F NMR (top) and ^{13}C NMR (bottom) spectra for **20**.

The peripheral side chain required for the preparation of **2** is 6-(4-(4-bromo-3-methyl-5-(4-*t*-butylphenyl)thiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine **(23)** (Scheme 2.5). The synthesis of **23** began with a regioselective coupling of **16** and alkyl boronic acid **9** to give 6-(4-(4-bromo-3-methylthiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine (**21**) as a viscous oil in a moderate yield (56%). Electrophilic bromination of **21** using NBS in glacial acetic acid produced 6-(4-(4,5-dibromo-3-methylthiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine **22** also in a moderate yield (48%). As discussed earlier, a common difficulty encountered during isolation is the susceptibility of the terminal amine to protonation under the acid-base extraction conditions. As a result, the compound was extracted into ethyl acetate after adjusting the pH to above 12. Subsequently, another Suzuki coupling reaction was carried out to couple **22** with *t*-butylphenyl boronic acid to obtain compound **23** in moderate yield (46%). The isolation of the product was initially challenging because **22** and **23** both contain a terminal amine and have very low R_f values. To overcome this situation, triethylamine was added to the mobile phase and elution by gravity helped to improve the separation of these compounds by silica gel column chromatography. Although **23** was isolated, the separation process was time-consuming and the multiple columns needed for purification is not economical. To overcome these challenges, I suggest that the terminal amine be introduced near the final step of the synthesis to reduce the extra steps required in purification.[64,65] Alternatively, Liao and coworkers synthesized 1-(2,5-dimethyl-3-thienyl)-2-(2-methyl-5-(*N,N*-dimethylaminophenyl)-3-thienyl)perfluorocyclopentene (**t**) at fairly good yield (60%).[69]



Scheme 2.5 Synthesis of **23**.

A similar DTE structure will be synthetically easier to prepare, although the organization of this amphiphile may differ in lipid vesicles. This is because the DTE core will most likely be positioned in the polar head group region thus membrane disruption may not be as effective.

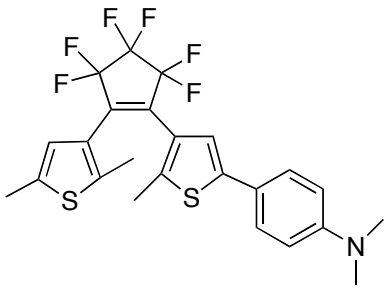
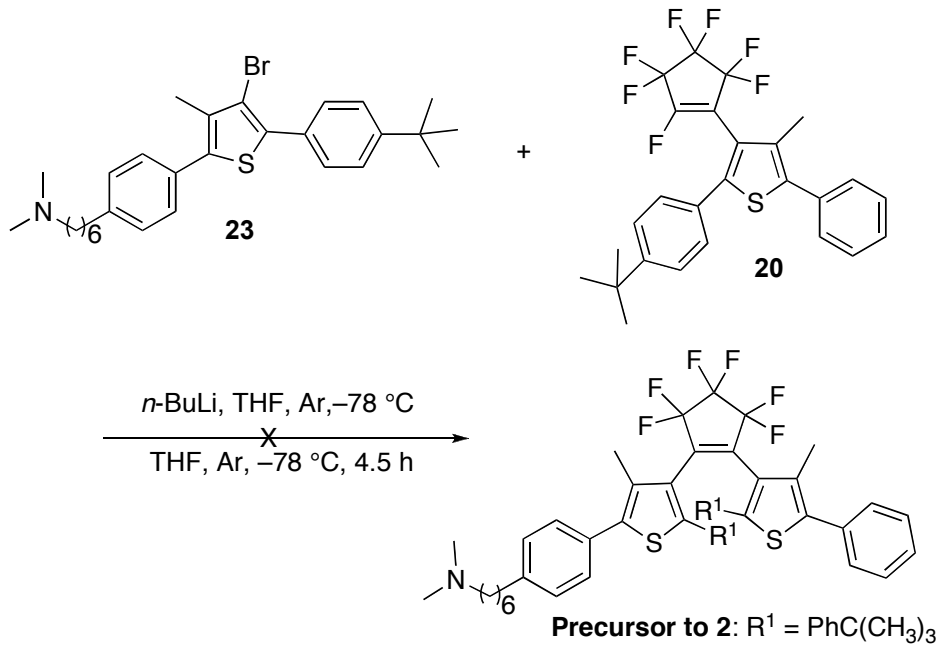


Figure 2.7 Chemical structure of **t**.

The coupling of **23** with **20** was expected to produce the precursor to **2** (Scheme 2.6). Unfortunately, this coupling was not successful. Instead, **20** was recovered in high yield (90%).



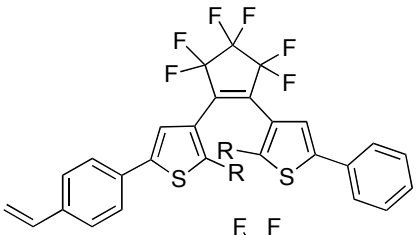
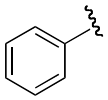
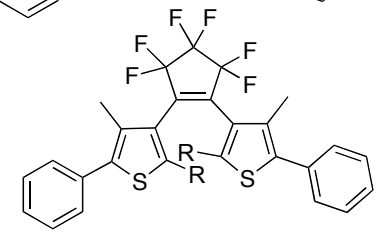
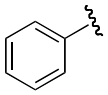
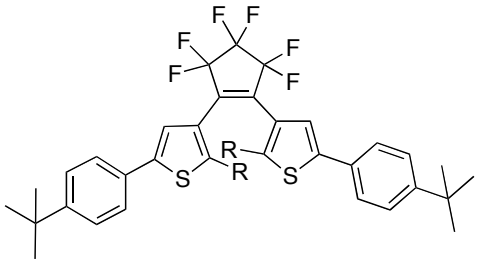
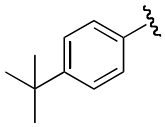
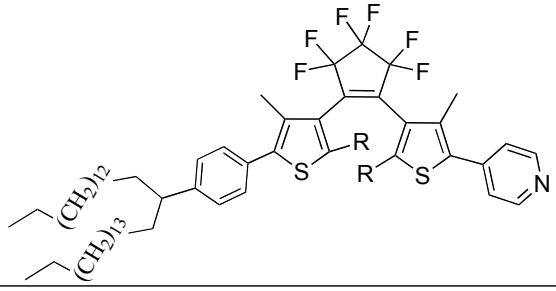
Scheme 2.6 Proposed synthesis of the precursor to **2**.

The initial lithium-halogen exchange reaction to generate the 3-thienyllithium intermediate appeared to have occurred given that **23** was recovered in its debrominated form. However, we hypothesize that the reaction of the carbanion intermediate with **20** was inhibited because of a steric effect. Specifically, this effect may arise from the presence of *t*-butylphenyl and methyl substituents at the alpha positions of the carbanionic carbon. Given the high yield of the recovered **20**, this means that the lithiated **23** was unable to react. The debrominated product was either formed from trace amounts of water in the reagents or during the work-up. In general, the early stage of the lithium-halogen reaction is usually marked by formation of a yellow solution lithiated

intermediate. The colour normally fades upon the addition of the perfluorocyclopentene derivative, but this was not a good indicator for this specific reaction, as **23** was also pale yellow and this colour persisted throughout the reaction.

To further support our hypothesis of a substituent effect, we have summarized the coupling yields of other symmetrical and asymmetrical DTEs that also proceed via a 3-thienyllithium intermediate with substituents alpha to the carbanionic carbon (Table 2.1). Branda and coworkers reported a coupling reaction yield of 45% for the preparation of an asymmetrical DTE with phenyl substituents at the 2– and 2'–positions (Table 2.1, entry 1).[46] Their yields were reduced to 17% when methyl substituents were introduced at the 4– and 4'–positions (Table 2.1, entry 2).[46] Branda also reported a coupling reaction yield of 15% for a symmetrical DTE with *t*-butylphenyl substituents at the 2– and 2'–positions.[46] Therefore, these results provide an upper limit for our reaction. Further, we suggest that a coupling yield no greater than 7.5% would be expected. This translates to approximately two milligrams of product under our experimental conditions. The probability of isolating this product is also lowered given several chromatography columns are often required during purification. As a result, it is not surprising that we were unable to isolate the precursor to **2**. Our group also reported a 23% yield for a branched alkyl chain pyridine DTE with methyl substituents at both reactive carbons and the 4– and 4'–positions (Table 2.1, entry 4).[49] The effect of the methyl substituents at the reactive carbon positions of this DTE was less evident compared the bulky *t*-butylpheny groups in the current work. In general, the combined effect of neighboring methyl and *t*-butylphenyl substituents of **23** are most likely responsible for suppressing its reactivity towards **20**.

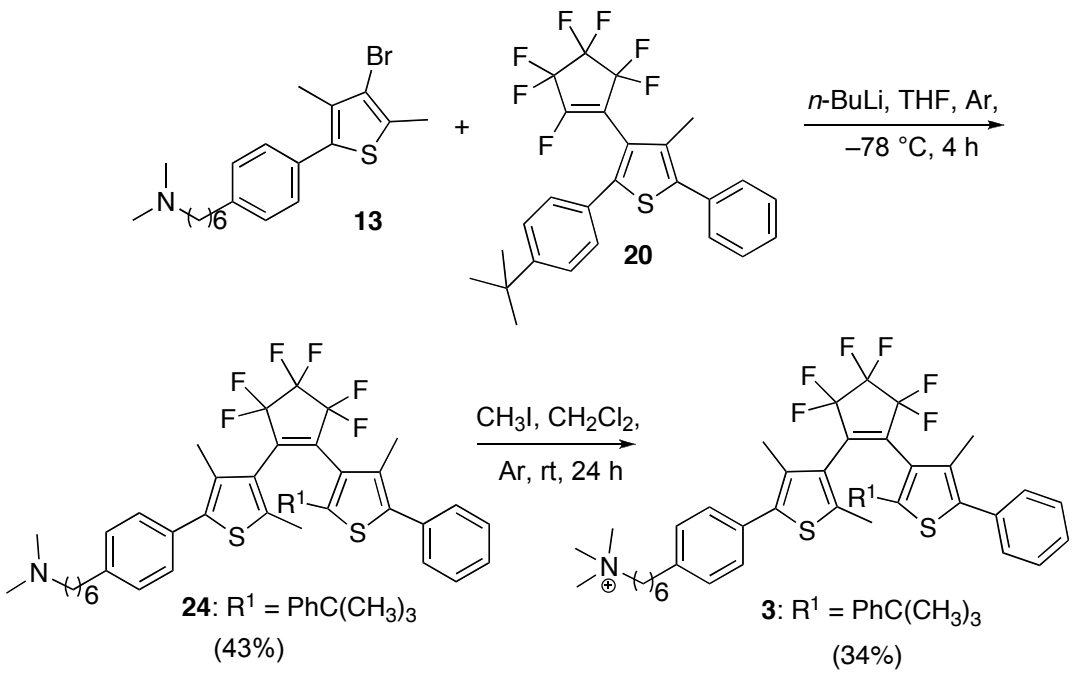
Table 2.1 Examples of DTEs with different substituents and their respective coupling yields.

Entries	DTE	R group	Yield
1			45%
2			17%
3			15%
4		Methyl	23%

2.4 Synthesis of 3

The outcome from the preceding section revealed an important structure-reactivity relationship that may be responsible for the low synthetic yields reported in many symmetrical and asymmetrical DTEs. Therefore, another rationale of this work was to explore this correlation further, as well as prepare a DTE that includes methyl substituents at the 4– and 4'–positions of the thiophene ring. As a result, we proposed to prepare 6-(4-(4-(2-(2-(4-*t*-butylphenyl)-4-methyl-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl)-3,5-dimethylthiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-ammonium iodide (**3**), which includes methyl substituents at the 2–, 4– and 4'–positions and a *t*-butylphenyl substituent at the 2'–position.

As shown in Scheme 2.8, the synthetic route for preparation of **3** involves the coupling of previously prepared intermediate products **13** and **20**. Fortunately, **24** was obtained in a moderate yield (43%). Interestingly, the coupling yield of **24** was about twice that of the branched alkyl chain DTE derivative presented in Table 2.1, entry 4,[49] yet 10% lower than the yield of the precursor to **1**. The latter comparison clearly shows that the introduction of a single *t*-butylphenyl substituent has a significant effect on the coupling reaction yield. Nonetheless, a successful coupling was attained. Notably, there was no evidence for the formation of debrominated **13**, in stark contrast to what was observed during our attempt to prepare the precusor to **2**. Finally, conversion of the tertiary amine to the quaternary ammonium salt gave **3** (34%).



Scheme 2.7 Synthesis of **3**.

As part of our structural analysis, a high resolution mass spectra (HRMS) of **3** was obtained as shown in Figure 2.8. This spectrum clearly shows molecular ions corresponding to the calculated values of M+ and M+1 ions. The calculated value for M+ is 809.0428, which is in accordance with the observed value of 808.3416. From the successful synthesis of **3**, it appears that the presence of a methyl group alpha to the carbanionic carbon does not significantly affect the coupling reaction provided the other neighboring substituent is small. However, to prepare a DTE with *t*-butylphenyl substituents at the reactive carbons we concede that the 4– and 4'–positions should be non-methylated.

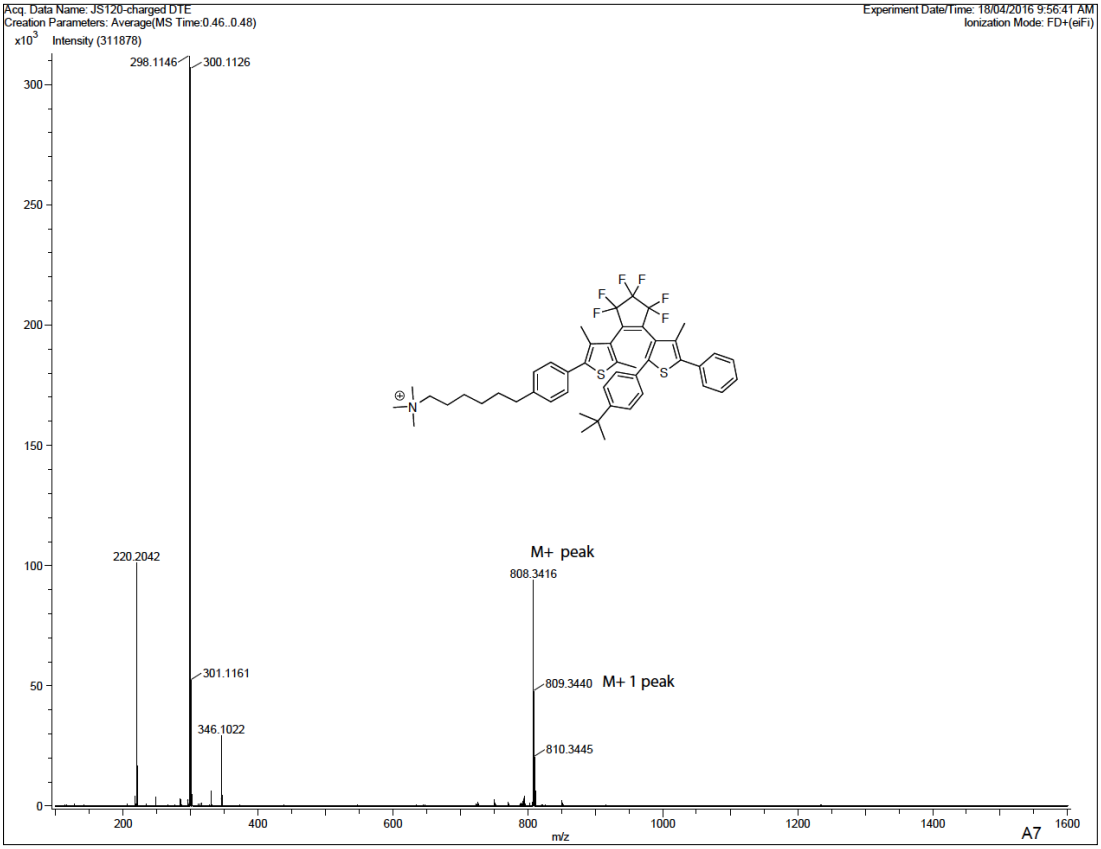
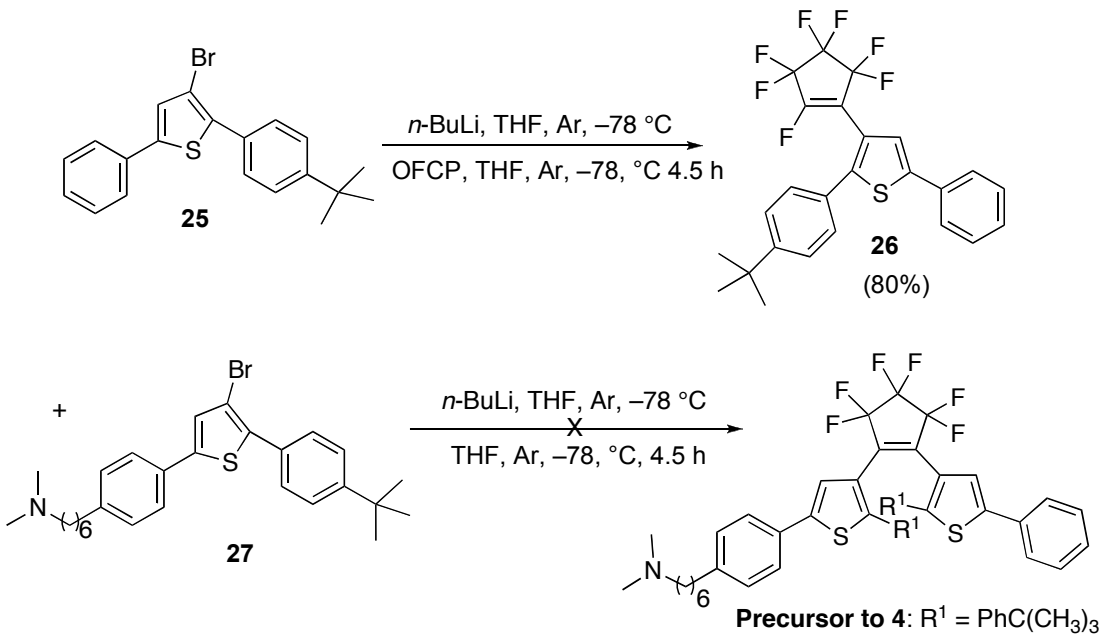


Figure 2.8. HRMS of **3**.

2.5 Synthesis of 4

The available data from the synthesis of **2** and **3** highlights the influence of steric factors on the DTE coupling efficiency. The final goal of this work was to forego the methyl substitution at the 4– and 4'–positions but allow for the introduction of bulky substituents at the reactive carbons while still including aspects of lipid complementarity. In order to achieve this goal, a DTE that incorporates *t*-butylphenyl substituents at both the 2– and 2'–positions was proposed. Given the successful synthesis of **3** and that Branda and coworkers had previously reported on the preparation of a similar DTE core with *t*-butylphenyl substituents at the 2– and 2'–positions (Table 2.1, entry 3), the synthesis of 6-(4-(5-(4-*t*-butylphenyl)-4-(2-(2-(4-*t*-butylphenyl)-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl) thiophen-2-yl)phenyl)-N,N-dimethylhexan-1-ammoniumiodide (**4**) was considered feasible.

Compound **4** was prepared in a similar manner as **2** and **3** except 2,4-dibromothiophene was used as a precursor to preclude methyl substitution at the 4– and 4'–positions (Scheme 2.8). The precursors **26** and **27** were synthesized as described for **20** and **23**, respectively. It was apparent that the percent yields resulting from these coupling reactions were strikingly different. The yields of **26** and **27**, which lack methyl substitution at the 4– and 4'–positions, were significantly higher (80% and 56%, respectively) than those of the methylated derivatives **20** and **23** (both 46%). To obtain the mono-substituted perfluorocyclopentene derivative **26**, compound **25** was lithiated and treated with OFCP. Notably, a symmetrical DTE **u** (Figure 2.9a) was recovered as a side product at a 15% yield.



Scheme 2.8 Proposed synthesis of the precursor to **4**.

The yield of this symmetrical DTE was comparable to the literature yield (Table 2.1, entry 3). The reason why **u** was recovered may have been due to a slight increase in the flow-rate during the drop-wise addition, leading to a double addition to OFCP.

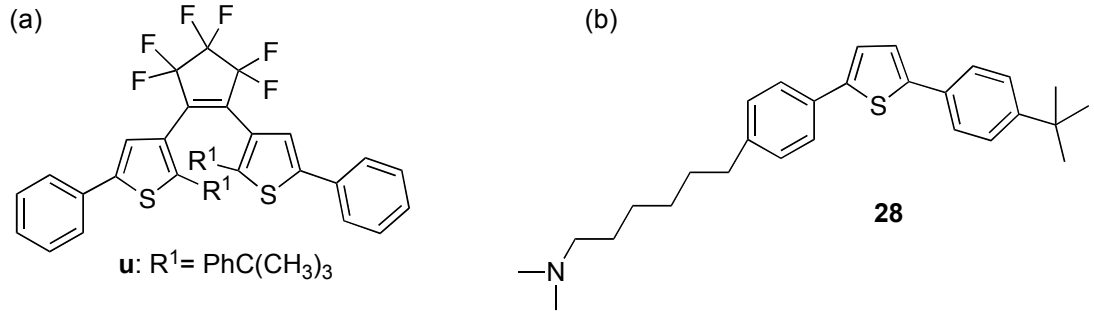


Figure 2.9 Chemical structures of **u** and **28**.

A comparison of ^{19}F NMR spectra of **u** with **26** shows a distinct change in their fluorine environments (Figure 2.10). There is a reduction in the number of peaks from four

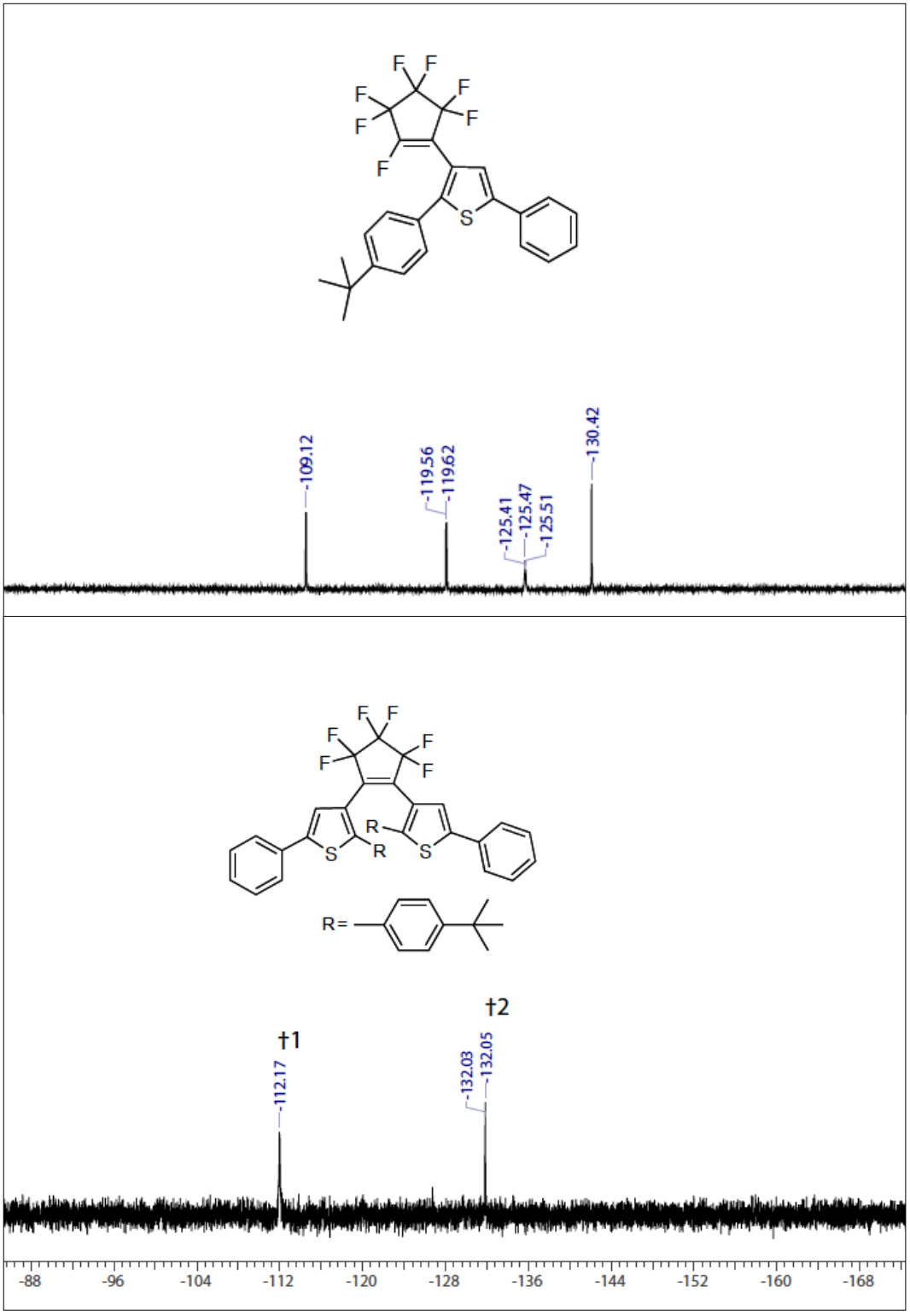


Figure 2.10 A comparison of ^{19}F NMR spectra of **26** (top) and **u** (bottom) in $CDCl_3$.

to two for **26** and **u** respectively. The two peaks at labeled †1 and †2 at 112.2 and 132.1 ppm (bottom spectra) were assigned to two sets of inequivalent fluorine atoms in **u**. The isolation of **u** was indicative that the coupling reaction is successful with *t*-butylphenyl substituents at the 2– and 2'–positions.

The coupling reaction of **26** with **27** was expected to produce the precursor to **4**. However, this coupling was not successful. Instead of the target product, a debrominated derivative of **27** (Figure 2.9b) was recovered in a high yield (60%). ^{1}H NMR and HRMS analysis confirmed the isolation of **28**. A comparison of the aromatic regions in the spectra of **27** and **28** is shown in Figure 2.11. The spectrum of **27** shows a singlet peak at 7.25 ppm, which overlaps with the solvent peak. This peak was assigned to the thiophene proton of **27**. After debromination, the bromine was replaced with hydrogen and two distinctive doublet peaks at 7.23 and 7.25 ppm, each with a coupling constant of 0.9 Hz were observed. These peaks were assigned to two thiophene protons of **28**. The ^{1}H NMR analysis supports the debromination of the starting material to give **28**.

The coupling reaction between **26** and **27** was attempted twice more, yet the precursor to **4** was not isolated. We suspect that a secondary substituent effect may be playing a role. Although, the methyl substituents were absent at the 4– and 4'–positions, we hypothesize that the coupling reaction yield may also be affected by the 4-(*N,N*-dimethylaminohexyl)phenyl substituent at the periphery of the thiophene. While the exact nature of this effect is currently unclear, we recently observed a similar effect in our group. As discussed earlier, the coupling reaction yield for an asymmetrical DTE with a branched alkyl chain was 23%.[49] This yield was one half of that reported by Meijera and coworkers for a symmetrical version of this DTE without an alky substituent at the

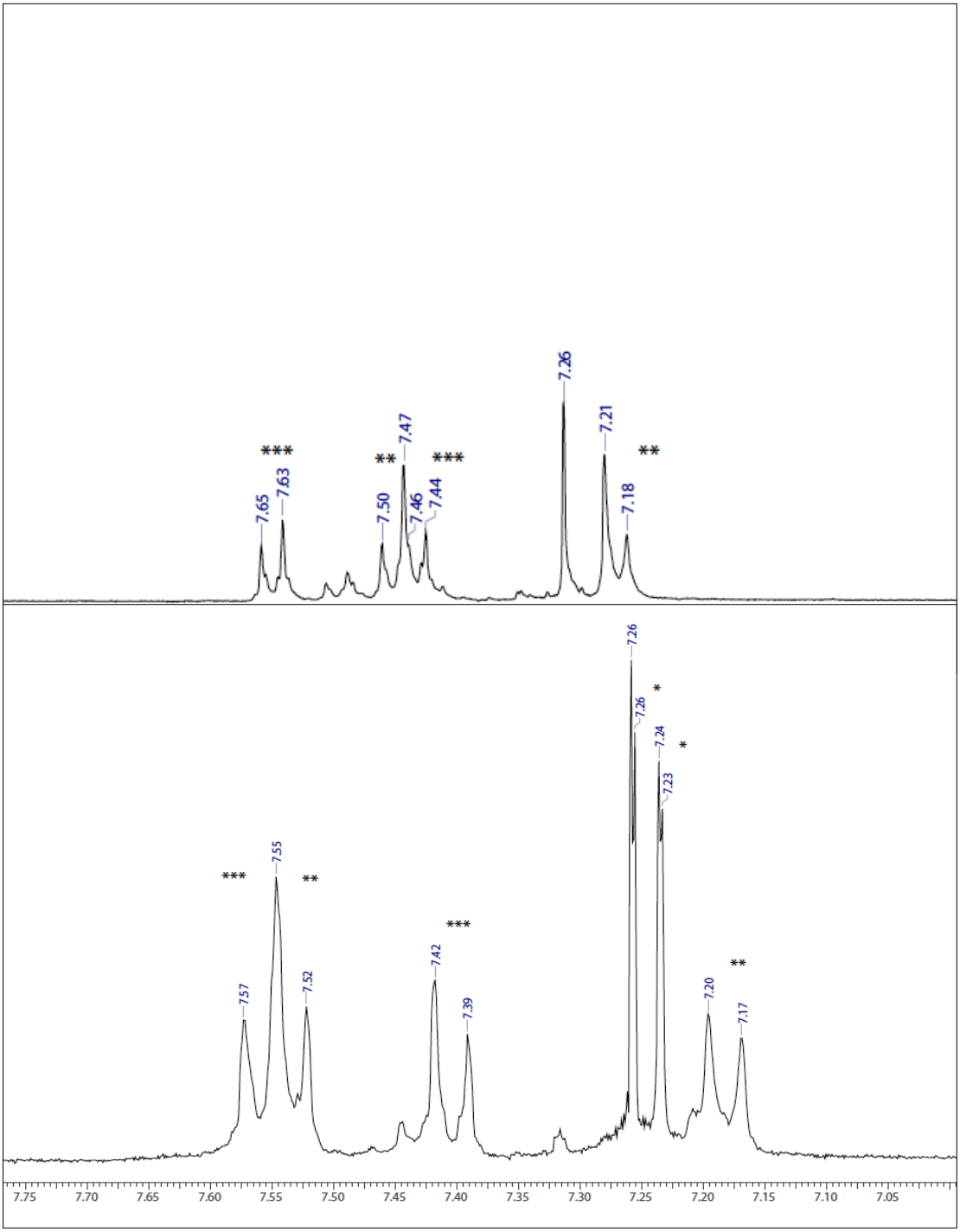


Figure 2.11 A comparison of the aromatic region of ^{1}H NMR spectra for **27** (top) and **28** (bottom) in $CDCl_3$. The peaks labeled with an asterisk represent the following proton environments: * thiophene; ** phenyl ring; *** *t*-butylphenyl ring.

periphery of thiophene.[51]

Thus, the alkyl substituent at the 5–position in **27** may reduce the coupling efficiency of **26** and **27**. Consequently, we suggest that like the precursor to **2**, a coupling yield no greater than 7.5% would be expected. This translates to approximately four milligrams of product under our experimental conditions. Similar to our attempts to prepare the precursor of **2**, the probability of isolating this product is also lowered given the challenges we have experienced during purification of aminoalkyl-containing compounds. For these syntheses to be viable one would have to increase the scale of the synthetic routes. Increasing the scale of this route would increase costs and potentially introduce new challenges. As a result, new synthetic routes should be devised to circumvent these difficulties, but retain some of the design principles explored.

2.6. Assessing the overall efficiency of our syntheses

There are several factors that contribute to the overall efficiency of a synthesis such as the price of the starting materials, and the time it takes to complete the synthesis.[72] For multi-step syntheses such as those developed in this work, the cost usually increases as the overall yield of the target compound decrease because more starting materials are required. In order to maximize the overall percent yield of a synthesis, the number of linear steps in the synthesis should be minimized, and each step should proceed with the highest possible percent yield. For example, a three-step linear synthesis which proceeds with an 85% yield will have an overall yield of $(0.85)^3 = 0.61$ or 61%, while a six-step linear synthesis will have an overall yield of 37%.

In this work, we attempted to enhance the overall synthetic yields by using a convergent synthesis where fragments of a target compound are synthesized separately in linear sequences and coupled together at a later stage. The two large fragments, namely the mono-substituted perfluorocyclopentene and the alkylamino-substituted thiophene derivatives, were synthesized in a linear sequence and convergently coupled to obtain the various DTE precursors. In a convergent synthesis, the longer linear sequence branch determines the overall yield.[72] For instance; the synthesis of the precursor of **1** requires eleven steps. However, the longest branch starting with the 6-aminohexanoic acid has six steps. Therefore, the overall yield of the precursor of **1** is 11% (i.e., (0.75)(1.00)(0.57)(0.81)(0.60)(0.52) = 0.11). Similarly, the synthesis of the precursor of **3** has thirteen steps and the longest branch has six steps. This translates to an overall yield of 9% (i.e., (0.75)(1.00)(0.57)(0.81)(0.60)(0.43) = 0.09). The overall yields of the precursors of **1** and **3** are comparable to that of a methyl derivative earlier reported in our group.[16] Although the overall synthetic yields are low for these DTEs, the final coupling yield between the two large fragments proceeded at moderate yields (53% and 43% for the precursors of **1** and **3**, respectively) thus producing a reasonable amount of the target compounds. On the other hand, the syntheses of the precursors of **2** and **4** both have eight steps in the longest branch. The overall yield of the precursors of **2** and **4** is estimated to be 0.4% (i.e., (0.75)(1.00)(0.57)(0.81)(0.56)(0.48)(0.46)(0.075) = 0.004). Compared with the precursors of **1** and **3**, the syntheses of the precursors of **2** and **4** have two additional steps, which lower the overall yield. Furthermore, the final coupling yield between the two large fragments in **2** and **4** is estimated to proceed at a significantly lower yield (7.5%) compared with 53% and 43% for the precursors of **1** and **3**, respectively. The

extremely low overall yield translates to less than a few milligrams of the final target compounds. Scaling up these synthetic routes would be necessary in order to recover reasonable quantities of **2** and **4** that are needed to examine their photochromism and their application in self-assemblies such as lipid vesicles. For instance, approximately 25 g of starting material would be required to obtain 100 mg of either **2** or **4** based on these estimated overall yields. This translates to a more than ten fold increase in scale for these syntheses. As a result, scaling up these synthetic routes would increase costs and time, given that some steps may require multiple batches before proceeding to the next step. In addition, scaling up reactions may introduce new challenges not observed at our current scales.

3.0 Conclusions

In summary, we have presented synthetic routes that were used to successfully prepare asymmetrical, amphiphilic DTEs **1** and **3**, and the intermediate products for **2** and **4**. During this work, a new synthetic method was explored to replace the expensive, palladium-catalyzed, reductive amination step. This method involved a modified Eschweiler–Clark reaction that uses formaldehyde as the reducing agent as well as the methylating agent.[62] We also investigated a strategy to improve the purification of boronic acid derivatives, which was especially effective for the preparation of phenylboronic acid. These exploratory studies show some promise but they need to be examined further to benefit the synthetic routes developed in this work.

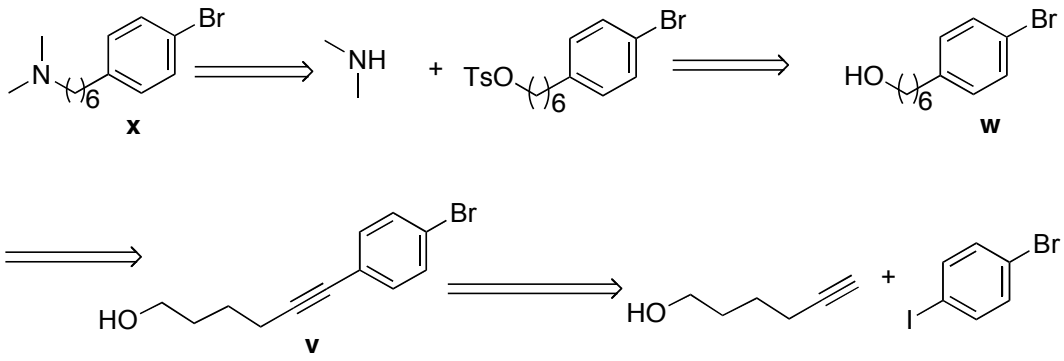
More importantly, we have uncovered an underreported substituent effect that has substantial influence on the efficiency of a key coupling reaction. In general, the presence of substituents at the 2–, 2'– and 4–, 4'–positions of the thiophene ring systems appears to lower the overall coupling reaction efficiency. Specially, the coupling yields are significantly reduced when a lithiated thiophene derivative that contain bulky substituents alpha to the position of the carbanionic carbon is reacted with a mono-substituted perfluorocyclopentene adduct also substituted at the 2'–position with a bulky substituent. These substituent effects were deemed primarily responsible for the unsuccessful preparation of **2** and **4**. It was found that replacing a *t*-butylphenyl group with a methyl group at one of the reactive carbons led to the successful synthesis of **3** presumably by reducing the steric hindrance during this coupling reaction. It was also hypothesized that the alkylammonium substituent at the periphery of the thiophene ring may be playing a

role in this coupling reaction, although the exact nature of this substituent effect is currently not well understood. As a result, in order to prepare a sufficient amount of **2** and **4** for further study, one would have to scale up these synthetic routes at least ten fold. However, increasing the scale of these syntheses will increase their cost, their preparation time, and will mostly likely present new challenges. Thus, the development of more strategic synthetic routes may be beneficial going forward.

4.0 Future Work

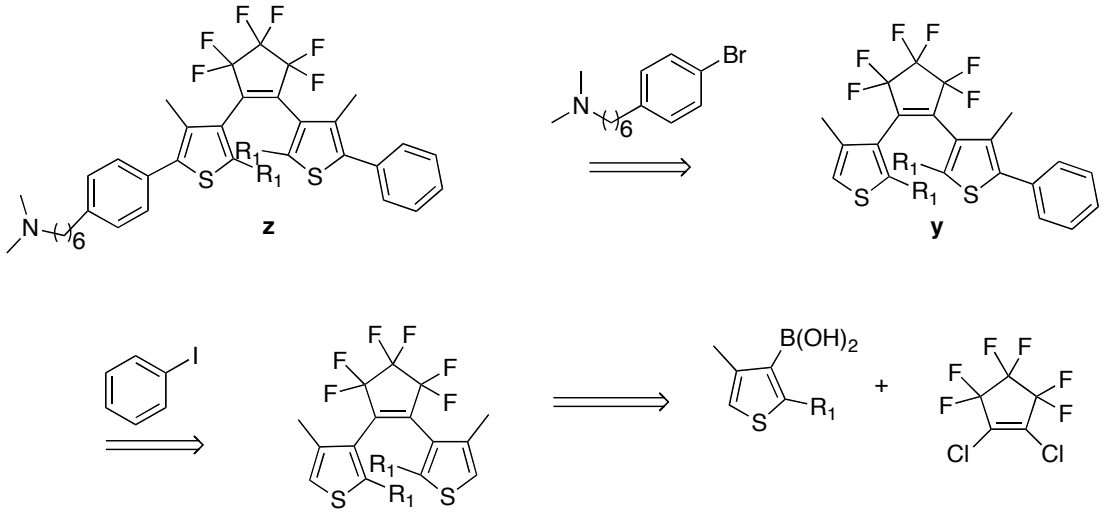
As discussed in this work, the *n*-BuLi/OFCP approach used for preparing DTEs does present some challenges. First, OFCP is expensive and highly volatile. Additionally, the substituents on the thiophene ring greatly decrease the overall coupling yield of the DTEs. Futhermore, our existing method of preparing the alkylamine substituent is challenging given the difficulties encountered during the purification of the amino-containing compounds. To circumvent these challenges, a two-path synthetic route for the preparation of asymmetrical amphiphilic DTEs that uses easily accessible starting materials is proposed.

The first part aims to introduce the terminal amine at the final steps of the synthesis, without affecting the integrity of the DTE backbone. This route is described in the retrosynthetic analysis presented in Scheme 4.1. The precursor 6-(4-bromophenyl)-5-hexyn-1-ol (**v**) is derived from a Sonogashira coupling of 5-hexyn-1-ol and 1-bromo-4-iodobenzene.[64] This is followed by a reduction of the triple bond to give 4-bromobenzenehexanol (**w**). The introduction of a tosyl group and subsequent heating in dimethylamine solution would give the 6-(4-bromophenyl)-*N,N*-dimethyhexan-1-amine (**x)**.[65] Although the hydroxyl group is ionizable, the isolation of intermediate products can easily be isolated with extraction and recrystallization.



Scheme 4.1 Potential retrosynthetic analysis to introduce the amino-substituent.

The second synthetic part takes advantage of the direct arylation methods proposed by Shinokubo and coworkers.[43] The highly volatile OFCP reagent is replaced with 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene. Suzuki cross coupling between the 1,2-dichloro-3,3,4,4,5,5-hexafluorocyclopentene and a preformed boronic acid-substituted thiophene yields a symmetrical DTE (Scheme 4.2).



Scheme 4.2 Proposed retrosynthetic pathway for **z**.

The symmetrical DTE is then subjected to a direct arylation with iodobenzene to yield an asymmetrical DTE (**y**). Further arylation with **x** prepared in Scheme 4.1 would give DTE **z**, which can then be methylated accordingly to give an asymmetrical amphiphilic DTE.

Once the target compounds are prepared, this research project will focus on the characterization of their photochromic reactivity and absorption properties. These DTEs will also be examined in lipid vesicles to assess their photocontrol of membrane permeability.

5.0 Experimental

5.1 Instrumentation

^{1}H, proton decoupled ^{13}C (i.e., $^{13}C\{^{1}H\}$), and proton decoupled ^{19}F (i.e., $^{19}F\{^{1}H\}$) NMR spectra were recorded at 300.18, 75.48 and 282.46 MHz, respectively, on a Varian Mercury plus NMR spectrometer. All chemical shifts are referenced to solvent signals. High-resolution mass spectral analysis was carried out by the University of Saskatchewan on an API Qstar XL mass spectrometer using field desorption (FD), and electron impact ionization modes.

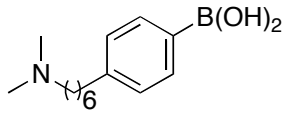
5.2 Materials

All reactants (99+%, Sigma-Aldrich), deuterated solvents (99.9 atom % D, Sigma-Aldrich), octafluorocyclopentene (99+%, SynQuest Laboratories), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (99.9+% Pd, Strem Chemicals) were purchased and used as received. Diethyl ether, 1,4-dioxane, dichloromethane, tetrahydrofuran, and triethylamine were purified following literature procedures.[73] Flash and gravity column chromatography was performed on silica gel (200-400 mesh, 60 Å, Sillicycle) or basic aluminum oxide (activated, 60 mesh, 58 Å, Alfa Aesar).

5.3 Synthetic Procedures

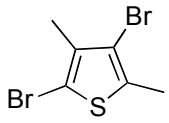
5.3.1 4-(6-(*N,N*-Dimethylamino)hexyl)phenylboronic acid (9)

The preparation of **9** and its starting material, 6-(4-bromophenyl)-*N,N*-dimethylhexan-1-amine (**8**; 57% in four steps), was based on published procedures.[37,62] Briefly, *n*-BuLi (3.6 mL of a 2.5 M solution in hexanes, 4.9 mmol) was added dropwise to a solution of **8** (1.12 g, 4.15 mmol) in tetrahydrofuran (THF) (30 mL) at –78 °C under an atmosphere of argon. After stirring for 1 h, trimethoxyborane (1.0 mL, 9.2 mmol) was added dropwise to the reaction mixture at –78 °C and the mixture was allowed to warm to room temperature. After stirring for 12 h, an aqueous solution of hydrochloric acid (20 mL, 2 M) was added and the mixture was stirred for another 20 min. The pH of the mixture was adjusted to 9 by addition of a saturated aqueous solution of sodium bicarbonate (15 mL) and was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a pale-yellow oil which was used without further purification in Suzuki cross coupling reactions with substituted thiophene derivatives.



5.3.2 2,4-Dibromo-3,5-dimethylthiophene (10)

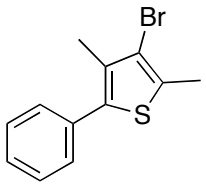
The preparation of **10** was based on a published procedure.[62] NBS (9.59 g, 53.9 mmol) was added to a solution containing 2,4-dimethylthiophene (2.75 g, 24.5 mmol) in a mixture of acetic anhydride (4.6 mL, 47 mmol) and glacial acetic acid (30.0 mL, 17.4 M). After stirring for 2 h at 80 °C, the reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with petroleum ether (3 × 30 mL). The combined organic extracts were then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (petroleum ether) gave **10** as a pale-yellow oil (4.25 g, 63%). ^{1}H NMR ($CDCl_3$, δ): 2.17 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 15.6, 16.3, 104.9, 111.6, 134.1, 136.5.



5.3.3 3-Bromo-2,4-dimethyl-5-phenylthiophene (11)

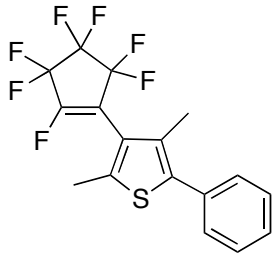
The preparation of **11** has been adapted from a previously published procedure.[35] Briefly, magnesium (1.70 g, 70.1 mmol) was added to bromobenzene (6.7 mL, 64 mmol) in THF (135 mL). The reaction mixture was stirred for 4 h at 70 °C. After cooling to –78 °C, the phenylmagnesium bromide was transferred via cannula into a –78 °C solution of trimethylborane (7.90 g, 76.4 mmol) in THF (100 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. The yellow solution was poured into

an aqueous solution of hydrochloric acid (150.0 mL, 2M). The solution was extracted with diethyl ether (100 mL × 3). The combined organic extracts were washed with an aqueous solution of sodium hydroxide (50 mL, 1 M) followed by hydrochloric acid (35 mL, 2 M). Recrystallization from methanol gave phenyl boronic acid as a white solid (mp 215–217 °C), which was used in the next step without further purification. Compound **10** (1.40 g, 5.00 mmol) and an aqueous solution of sodium carbonate (10.0 mL, 2.0 M) were added consecutively in a dropwise manner to a mixture of phenylboronic acid (0.62 g, 5.0 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.13 mmol) in 1,4-dioxane (30 mL) under an atmosphere of argon. After stirring at 100 °C for 5 h, the reaction mixture was allowed to cool to room temperature, diluted with water (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (3 × 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (2:1 diethyl ether/petroleum ether) and recrystallization from methanol gave pure **11** as a white solid (1.07 g, 88%). ^{1}H NMR ($CDCl_3$, δ): 2.27 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.32–7.41 (m, 5H, Ar H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ): 15.4, 15.8, 113.9, 127.7, 128.6, 129.2, 132.5, 132.7, 132.6, 145.7.



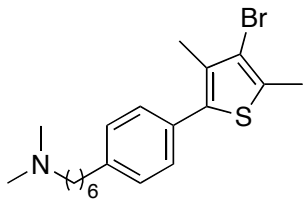
5.3.4 3-(2,3,3,4,4,5,5-Heptafluorocyclopent-1-enyl)-2,4-dimethyl-5-phenylthiophene (12)

The preparation of **12** has been adapted from a previously published procedure.[62] *n*-BuLi (0.6 mL of a 1.4 M solution in hexanes, 0.84 mmol) was added dropwise to solution **11** (0.20 g, 0.74 mol) in THF (10 mL) at –78 °C under an atmosphere of argon. The reaction mixture was stirred for 30 min then added dropwise via a cannula to a stirred solution of OFCP (1.10 g, 5.24 mol) in THF (7.0 mL) at –78 °C. The reaction was stirred for 4 h then cooled to room temperature. Hydrochloric acid (2.0 mL of 6.0 M aqueous solution, 12 mmol) was added to the mixture after another 2 h. A saturated aqueous solution of sodium carbonate (1.0 mL, 2.1 M) was added to neutralize the mixture. The organic layer was extracted with petroleum ether (3 × 20 mL) and washed with a saturated solution of sodium chloride (60 mL). The organic extract was dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether) gave **12** as a white solid (0.21 g, 75%). ^{1}H NMR ($CDCl_3$, δ): 2.12 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.32–7.41 (m, 5H, Ar H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 12.7, 12.9, 119.8, 126.7, 127.6, 128.2, 130.9, 132.7, 135.7, 139.1. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, δ): –108.8 (m, 2F), –119.5 (m, 2F), –127.0 (m, 1F), –130.8 (m, 2F).



5.3.5 6-(4-(4-Bromo-2,5-dimethylthiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine (13)

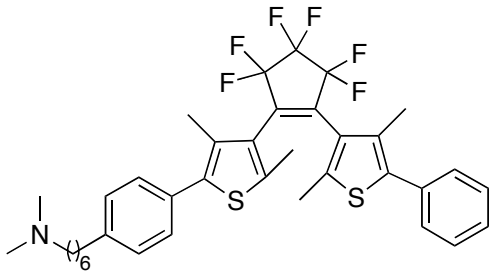
The preparation of **13** has been adapted from a previously published procedure.[62] Compound **9** (0.575 g, 2.48 mmol) and sodium carbonate (4.5 mL of 2.0 M aqueous solution, 9.00 mmol) were added consecutively in a dropwise manner to a stirred mixture of boronic acid **9** (0.56 g, 2.2 mmol) and $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) in 1,4-dioxane (20 mL) under an atmosphere of argon. After stirring for 6 h at 100 °C, the reaction was cooled to room temperature, diluted with water (20 mL) and extracted into ethyl acetate (3 × 35 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (60 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (7:1 chloroform/methanol) gave **13** as a yellow solid (0.38 g, 60%) ^{1}H NMR ($CDCl_3$, δ): 1.36 (m, 4H, CH_2), 1.45 (m, 2H, CH_2), 1.65 (m, 2H, CH_2) 2.21 (s, 6H, CH_3), 2.53 (s, 3H, CH_3), 2.27 (t, J = 7.2 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.63 (t, J = 7.2 Hz, 2H, CH_2), 7.19–7.21 (m, 2H, Ar H), 7.40–7.42 (m, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 15.4, 15.8, 27.4, 29.4, 31.5, 35.8, 45.3, 51.0, 59.8, 113.8, 128.5, 128.6, 128.8, 129.1, 132.2, 134.9, 142.4. HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{20}H_{28}{}^{79}BrNS$, 393.1126; found 393.1114.



5.3.6 6-(4-(4-(2-(2,4-Dimethyl-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl)-3,5-dimethylthiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-amine (14)

The preparation of **14** has been adapted from a previously published procedure.[62] Briefly, *n*-BuLi (0.32 mL of a 1.4 M solution in hexanes, 4.4 mmol) was added dropwise to a solution of **13** (0.16 g, 4.0 mmol) in THF (6.0 mL) at –78 °C under an atmosphere of argon. After stirring for 30 min, a solution of **12** (0.152 g, 4.13 mmol) in THF (6.0 mL) was added to the reaction mixture dropwise via cannula at –78 °C. The mixture was stirred for an additional 4 h at –78 °C and allowed to warm to room temperature. Hydrochloric acid (2.5 mL of 2.0 M aqueous solution, 5.0 mmol) was added to the reaction after 2 h and stirred for 10 min. The reaction mixture was diluted with water (15 mL) and a saturated aqueous solution of sodium carbonate (15 mL) was added to adjust the pH to 12. The organic layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification of the crude product by column chromatography (10:1:0.1 ethyl acetate/methanol/triethylamine) gave **14** as a white solid (0.12 g, 52%). ^{1}H NMR ($CDCl_3$, δ): 1.33 (m, 4H, CH_2), 1.46 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.05 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.21 (s, 6H, CH_3), 2.25 (t, J = 7.2 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.59 (t, J = 7.8 Hz, 2H, CH_2), 7.17–7.20 (m, 2H, Ar H), 7.25–7.28 (m, 2H, Ar H), 7.30–7.41 (m, 5H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 14.9, 15.2, 27.5, 27.2, 29.5, 31.5, 35.8, 45.6, 60.1, 127.6, 128.7, 128.8, 129.2, 129.4, 131.6, 134.3, 136.4, 136.6, and 142.4. ^{19}F{^{1}H} NMR ($CDCl_3$, δ): –110.4 (m, 4F), –132.1 (m, 2F). HRMS–FD (*m/z*): $[M]^+$

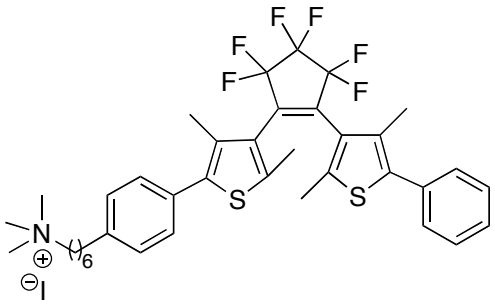
calcd for $C_{37}H_{39}F_6NS_2$, 675.2428; found 675.2432.



5.3.7 6-(4-(4-(2-(2,4-Dimethyl-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl)-3,5-dimethylthiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-ammonium iodide (1)

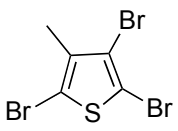
The preparation of **1** has been adapted from a previously published procedure.[62] Iodomethane (0.30 g, 2.1 mol) was added to a solution of **14** (0.095 g, 0.14 mmol) in dry dichloromethane (5 mL) and stirred for 24 h at room temperature. Dichloromethane was removed under reduced pressure, and the residue was washed with diethyl ether (3 × 20 mL). Recrystallization of the precipitate from dichloromethane/diethyl ether gave **1** as colorless solid (0.082 g, 76%). ^{1}H NMR ($CDCl_3$, δ): 1.43 (m, 4H, CH_2), 1.56 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.59 (t, J = 7.8 Hz, 2H, CH_2), 3.42 (s, 6H, CH_3), 3.52 (m, 2H, CH_2), 7.17–7.20 (m, 2H, Ar H), 7.20–7.28 (m, 2H, Ar H), 7.36–7.41 (m, 5H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 13.7, 13.9, 14.2, 22.1, 24.1, 27.6, 29.9, 29.9, 34.3, 52.7, 66.2, 126.4, 127.5, 127.6, 128.1, 128.6, 128.6, 130.5, 133.0, 135.2, 136.4, 139.8 and 140.6. ^{19}F{^{1}H} NMR ($CDCl_3$, δ): –110.4 (m,

4F), –132.3 (m, 2F). HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{38}H_{42}F_6NS_2$, 690.2659; found 690.2660.



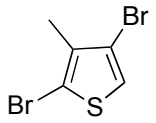
5.3.8 2,4,5-Tribromo-3-methylthiophene (15)

The preparation of **15** was adapted from a previously published procedure.[62] A mixture of bromine (71.5 g, 0.450 mol) and 48% aqueous solution of hydrogen bromide (40 mL) was added dropwise to mixture of 3-methylthiophene (12.7g, 129 mmol), 48% aqueous solution of hydrogen bromide (45 mL), and diethyl ether (40 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then refluxed for 3 h at 50 °C. The biphasic mixture was extracted with dichloromethane (3 × 150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether) and recrystallization from dichloromethane/methanol gave **15** as a colorless solid (13.0 g, 57%). ^{1}H NMR ($CDCl_3$, δ): 2.24 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ): 17.0, 108.2, 109.3, 116.6 and 137.4.



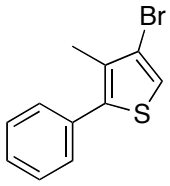
5.3.9 2,4-Dibromo-3-methylthiophene (16)

Preparation of **16** has been adapted from a previously published procedure.[62] *n*-BuLi (6.68 mL of a 2.5 M solution in hexanes, 16.7 mmol) was added dropwise to a solution of **15** (5.59 g, 16.7 mmol) in THF (75 mL) at –78 °C under an atmosphere of argon. After stirring for 15 min, the reaction mixture was poured into ice-cold water (75 mL) to give a biphasic mixture. The mixture was extracted with diethyl ether (3 × 60 mL), washed with water (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (petroleum ether) gave **16** as a colorless liquid (3.70 g, 87%). ^{1}H NMR ($CDCl_3$, δ): 2.29 (s, 1H, CH_3), 7.25 (s, 1H, Ar H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 15.5, 109.2, 112.2, 122.6 and 136.6.



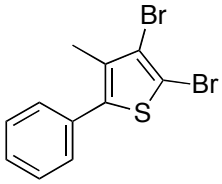
5.3.10 4-Bromo-3-methyl-2-phenylthiophene (17)

This method is similar to that used for **11**. Purification of the crude product by flash column chromatography (petroleum ether) gave **17** as a colorless solid (1.84 g, 74%). ^{1}H NMR ($CDCl_3$, δ): 2.29 (s, 3H, CH_3), 7.25 (s, 1H, Ar H), 7.41–7.44 (m, 5H, Ar H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 15.0, 114.4, 121.2, 128.1, 128.9, 129.3, 132.6, 134.6 and 138.7. HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{11}H_9{}^{79}BrS$, 251.9608; found 251.9619.



5.3.11 2,3-Dibromo-4-methyl-5-phenylthiophene (18)

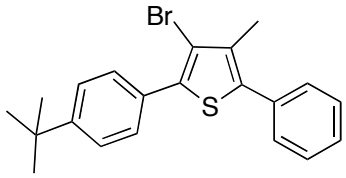
This method is similar to that used for **10**. Purification of the crude product by flash column chromatography (petroleum ether) gave **18** as a colorless solid (0.71 g, 92% yield). ^{1}H NMR ($CDCl_3$, δ): 2.30 (s, 3H, CH_3), 7.37–7.44 (m, 5H, Ar H). $^{13}C\{^{1}H\}$ ^{13}C NMR ($CDCl_3$, δ): 16.3, 109.4, 118.3, 128.4, 128.9, 129.3, 133.2, 133.8 and 139.1. HRMS–-FD (*m/z*): $[M]^+$ calcd for $C_{11}H_8{}^{79}Br_2S$, 329.8714; found 329.8717.



5.3.12 3-Bromo-2-(4-*t*-butylphenyl)-4-methyl-5-phenylthiophene (19)

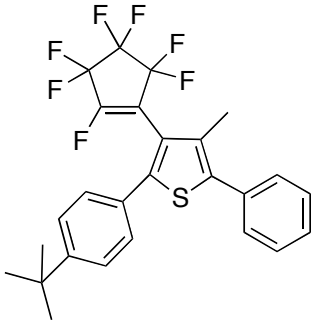
Preparation of **19** has been adapted from a previously published procedure.[62] Compound **18** (0.94 g, 2.8 mol) and sodium carbonate (5.6 ml of a 2.0 M aqueous solution, 11 mmol) were added consecutively in a dropwise manner to a mixture of *t*-butylphenylboronic acid (0.50 g, 2.8 mmol) and $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) in 1,4-dioxane (25 mL) under an atmosphere of argon. The reaction mixture was stirred at 100 °C for 8 h then cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (3 × 25

mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (40 mL) dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether) gave **19** as a white solid (0.69 g, 63 %). ^{1}H NMR ($CDCl_3$, δ): 1.37 (s, 9H, CH_3), 2.35 (s, 3H, CH_3) 7.29–7.48 (m, 7H, Ar H), 7.60–7.7.64 (m, 2H, Ar H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 16.0, 31.5, 34.9, 111.8, 119.7, 125.7, 128.0, 128.9, 129.3, 130.7, 133.8, 134.5, 137.1 and 151.4. HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{21}H_{21}{}^{79}BrS$, 384.0547; found 384.0544.



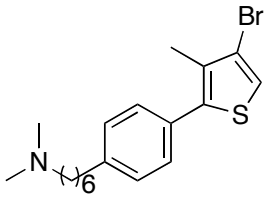
5.3.13 2-(4-*t*-Butylphenyl)-3-(2,3,3,4,4,5,5-heptafluorocyclopenten-1-yl)-4-methyl-5-phenylthiophene (20)

This method is similar to that used for **12**. Purification of the crude product by flash column chromatography (petroleum ether) gave **20** as a white solid (0.09g, 46% yield). ^{1}H NMR ($CDCl_3$, δ): 1.35 (s, 9H, CH_3), 2.20 (s, 3H, CH_3) 7.38–7.42 (m, 2H, Ar H), 7.44–7.48 (m, 3H, Ar H), 7.53–7.55 (m, 2H, Ar H), 7.61–7.64 (m, 2H, Ar H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 12.9, 30.2, 33.7, 118.0, 124.7, 127.0, 127.7, 128.3, 128.8, 131.8, 132.6, 137.8, 144.1 and 151.0. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, δ): –109.1 (m, 2F), –119.6 (m, 2F) – 125.5 (m, 1F), –130.4 (m, 2F). HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{26}H_{21}F_2S_1$, 498.1252; found 498.1241.



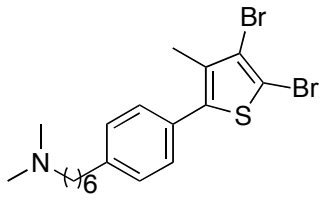
5.3.14 6-(4-(4-Bromo-3-methylthiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-amine (21)

This method is similar to that used for **13**. Purification of the crude product by flash column chromatography (7:1 chloroform/methanol) gave **21** as a pale yellow oil (0.23 g, 56%). ^{1}H NMR ($CDCl_3$, δ): 1.36 (m, 4H, CH_2), 1.48 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.22 (s, 6H, CH_3), 2.25 (t, J = 7.3, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.64 (t, J = 7.5 Hz, 2H, CH_2), 7.21–7.24 (m, 3H, Ar H), 7.29–7.34 (m, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 15.0, 27.6, 28.0, 29.5, 31.5, 35.8, 45.8, 60.0, 114.3, 120.8, 128.9, 129.1, 131.9, 132.3, 138.9 and 142.9.



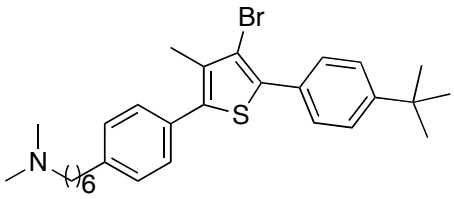
5.3.15 6-(4-(4,5-Dibromo-3-methylthiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine (22)

Preparation of **22** has been adapted from a previously published procedure.[62] NBS (0.13 g, 0.72 mmol) was added to a solution containing **21** (0.23 g, 0.59 mmol) in a mixture of acetic anhydride (2.4 mL, 24.7 mmol) and glacial acetic acid (0.6 mL, 10 mol). After stirring for 3 h, at 80 °C, the reaction mixture was allowed to cool to room temperature, diluted with water (5 mL). A saturated aqueous solution of sodium carbonate (10 mL) was added to adjust the pH to above 12. The organic layer was extracted with ethyl acetate (3 × 15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (10:1:0.1 ethyl acetate/methanol/triethylamine) gave **22** as a pale yellow oil (0.155 g, 48%). ^{1}H NMR ($CDCl_3$, δ): 1.36 (m, 4H, CH_2), 1.43 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 2.22 (s, 6H, CH_3), 2.25 (t, J = 7.2, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.64 (t, J = 7.5 Hz, 2H, CH_2), 7.21–7.24 (m, 2H, Ar H), 7.29–7.34 (m, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 16.3, 27.5, 27.8, 29.5, 29.5, 31.5, 35.9, 45.8, 60.1, 108.9, 118.2, 129.0, 129.1, 131.1, 132.9, 139.3 and 143.4.



5.3.16. 6-(4-(4-Bromo-3-methyl-5-(4-*t*-butylphenyl)thiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine (23)

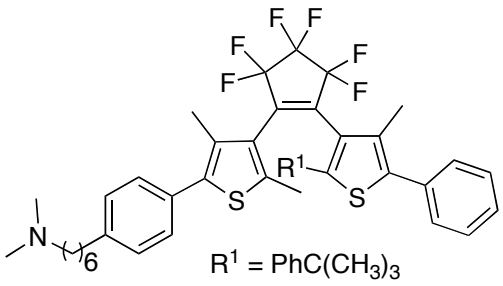
This method is similar to that used for **13**. The crude product was purified by flash column chromatography (10:1:0.1 ethyl acetate/methanol/triethylamine) to obtain **23** as a pale yellow oil (81 mg, 46 %). ^{1}H NMR ($CDCl_3$, δ): 1.36 (s, 9H, CH_3), 1.36 (m, 4H, CH_2), 1.42 (m, 2H, CH_2), 1.69 (m, 2H, CH_2), 2.22 (s, 6H, CH_3), 2.27 (t, *J* = 7.3, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.65 (t, *J* = 7.5 Hz, 2H, CH_2), 7.25–7.22 (d, *J* = 7.8, 2H, Ar H), 7.36–7.38 (d, *J* = 7.8, 2H, Ar H), 7.44–7.47 (d, *J* = 8.4, 2H, Ar H), 7.61–7.64 (d, *J* = 8.4, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 14.1, 26.3, 26.7, 28.3, 30.2, 30.4, 30.5, 34.6, 44.4, 58.8, 124.1, 124.4, 127.2, 127.5, 128.0, 128.1, 128.8, 140.8 and 148.6.



5.3.18 6-(4-(4-(2-(2-(4-*t*-Butylphenyl)-4-methyl-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl)-3,5-dimethylthiophen-2-yl)phenyl)-*N,N*-dimethylhexan-1-amine (24)

This method is similar to that used for **14**. Purification of the crude product by flash column chromatography (10:1:0.1 ethyl acetate/methanol/triethylamine) gave **24** as a white solid (48 mg, 43%). ^{1}H NMR ($CDCl_3$, δ): 1.33 (s, 9H, CH_2), 1.36 (m, 4H, CH_2), 1.43 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.79 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.33 (s, 6H,

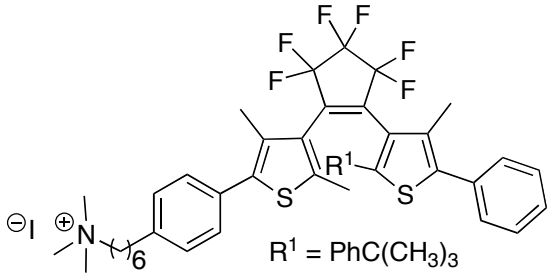
CH_3), 2.35 (s, 3H, CH_3), 2.38 (m, 2H, CH_2), 2.60 (m, 2H, CH_3), 7.01–7.04 (d, J = 8.4 2H, Ar H), 7.09–7.12 (m, J = 8.4, 2H, Ar H), 7.17–7.16 (m, 3H, Ar H), 7.19–7.22 (d, J = 8.4, 2H, Ar H), 7.34–7.7.37 (d, J = 8.4, 2H, Ar H), 7.45–7.47 (m, 2H, Ar H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ): 13.0, 13.2, 26.2, 28.1, 28.4, 30.1, 30.2, 34.5, 44.0, 58.6, 124.7, 126.7, 127.3, 127.5, 127.6, 127.8, 128.3, 129.5, 130.6, 132.9, 137.9, 140.8, 150.3 and 150.7. $^{19}F\{^1H\}$ NMR ($CDCl_3$, δ): –110.4 (m, 4F), –132.3 (m, 2F). HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{46}H_{49}F_6N_1S_2$, 793.3212; found 793.3210.



5.3.19 6-(4-(4-(2-(2-(4-*t*-Butylphenyl)-4-methyl-5-phenylthiophen-3-yl)-3,3,4,4,5,5-hexafluorocyclopent-1-enyl)-3,5-dimethylthiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-ammonium iodide (3)

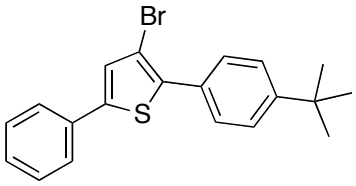
This method is similar to that used for compound **1** (30 mg, 34 %). ^1H NMR ($CDCl_3$, δ): 1.33 (s, 9H, CH_2), 1.42 (m, 4 H, CH_2), 1.56 (s, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.79 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.33 (s, 6H, CH_3), 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.60 (m, 2H, CH_3), 3.42 (s, 6H, CH_3), 3.60 (M, 2H, CH_2), 7.03-7.05 (m, 2H, Ar H), 7.07–7.18 (m, 5H, Ar H), 7.35–7.40 (m, 4H, Ar H), 7.41–7.46 (m, 2H, Ar H). $^{13}C\{^1H\}$ NMR ($CDCl_3$,

δ): 15.2, 15.4, 23.3, 26.1, 28.9, 31.2, 35.5, 53.9, 67.3, 128.8, 128.8, 129.8, 132.7, 132.9, 137.6 and 141.1. $^{19}F\{^{1}H\}$NMR ($CDCl_3$, δ): –110.4 (m, 4F), –132.3 (m, 2F). HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{47}H_{52}F_6NS_2$, 808.3445; found 808.3416.



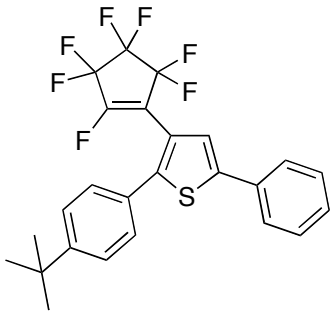
5.3.20 3-Bromo-2-(4-*t*-butylphenyl)-5-phenylthiophene (25)

This method is similar to that used for **19**. The starting material 2,3-dibromo-5-phenylthiophene was synthesized following a reported literature procedure (75% yield in five steps).[37] Purification by flash column chromatography (petroleum ether) obtained **25** as a white solid (1.39 g, 84 %). ^1H NMR ($CDCl_3$, δ): 1.38 (s, 9H, CH_3), 7.13 (s, 1H, Ar H), 7.38–7.43 (m, 3H, Ar H), 7.45–7.48 (m, 2H, Ar H), 7.57–7.60 (m, 2H, Ar H), 7.64–7.68 (m, 2H, Ar H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, δ): 31.6, 35.0, 107.8, 125.8, 125.8, 125.9, 127.7, 128.4, 128.7, 128.9, 128.9, 129.3, 130.2, 133.8, 137.1, 143.1 and 151.6.



5.3.21 2-(4-*t*-Butylphenyl)-3-(2,3,3,4,4,5,5-perfluorocyclopenten-1-yl)-5-phenythiophene (26)

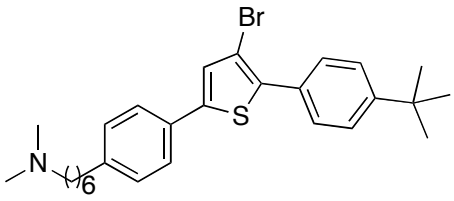
This method is similar to that used for **12**. Purification of the crude product by flash column chromatography (petroleum ether) gave **26** as a white solid (0.28 g, 80% yield). ^{1}H NMR ($CDCl_3$, δ): 1.38 (s, 9H, CH_3), 7.29 (s, 1H, Ar H), 7.32–7.40 (m, 5H, Ar H), 7.42–7.45 (m, 2H, Ar H), 7.60–7.63 (m, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 30.2, 33.7, 117.9, 122.0, 124.7, 124.8, 124.9, 126.6, 127.3, 127.9, 128.1, 128.7, 132.1, 143.6, 146.4 and 151.3. ^{19}F{^{1}H} NMR ($CDCl_3$, δ): –130.4 (m, 2F), –125.4 (m, 1F, –119.5 (m, 2F), –109.1 (m, 2F). HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{25}H_{19}F_7S_1$, 484.1096; found 484.1103.



5.3.22 6-(4-(4-Bromo-5-(4-*t*-butylphenyl)thiophen-2-yl)phenyl)-*N*,*N*-dimethylhexan-1-amine (27)

This method is similar to that used for **13**. Purification by flash column chromatography (10:1:0.1 ethyl acetate/methanol/triethylamine) gave **27** as a pale yellow viscous oil (0.24 g, 56 %). ^{1}H NMR ($CDCl_3$, δ): 1.36 (s, 9H, CH_3), 1.37 (m, 4H, CH_2), 1.42 (m, 2H, CH_2),

1.69 (m, 2H, CH_2), 2.22 (s, 6H, CH_3), 2.27 (t, J = 7.3, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.65 (t, J = 7.5 Hz, 2H, CH_2), 7.18–7.21 (m, 3H, Ar H), 7.44–7.46 (m, 2H, Ar H), 7.47–7.50 (m, 2H, Ar H), 7.63–7.66 (m, 2H, Ar H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ): 25.6, 26.1, 28.0, 30.1, 30.3, 33.7, 34.6, 43.7, 58.3, 117.8, 120.8, 124.4, 125.9, 125.9,127.4, 127.9, 128.0, 128.9, 129.7, 135.9, 141.9 and 150.3. HRMS–FD (*m/z*): $[M]^+$ calcd for $C_{28}H_{36}{}^{79}BrNS$, 497.1752; found 497.1764.



6.0. References

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(2) Brown, G. *Photochromism*; 1st ed.; Wiley-Interscience: New York, 1971.

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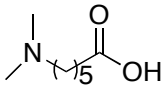
Appendix A

A.1 Procedures for synthesis of known compounds

A.1.1 6-(*N,N*-Dimethylamino)hexanoic acid (5)

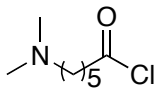
The preparation of **5** has been adapted from a previously published procedure.[62] A 37% aqueous solution of formaldehyde (6.0 mL, 0.42 mol) was added dropwise to a stirred suspension of 6-aminohexanoic acid (7.01 g, 53.1 mmol) and palladium on charcoal (7.00 g, 10 wt %) in water (300 mL) under an atmosphere of hydrogen gas (4 L). The reaction was stirred at room temperature for 12 h with a continuous supply of hydrogen gas. After the reaction was complete, the mixture was vacuum filtered through methanol, washed and concentrated under reduce pressure. Purification by flash column chromatography gave **8** as a colorless solid (6.10 g, 75%). ^{1}HNMR ($CDCl_3$, δ): 1.32 (m, 2H, CH_2), 1.58 (m, 4H, CH_2), 2.19 (t, J= 7.3 Hz, 2H, CH_2), 2.44 (s, 6H, CH_3), 2.64 (t, J= 8 Hz, 2H, CH_2), 12.0 (1H, CO_2H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 25.2, 26.9, 36.1, 43.2, 58.0, and 179.



A.1.2 6-(*N,N*-Dimethylamino)hexanoyl chloride (6)

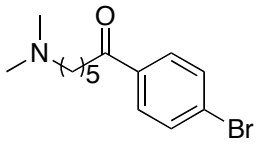
The preparation of **6** has been adapted from a previously published procedure.[62] Thionyl chloride (64.0 mL, 88.0 mmol) was added dropwise to **5** (11.8 g, 74.1 mmol). The

reaction was refluxed at 75 °C for 3 h under an argon atmosphere. Residual thionyl chloride was removed under reduced pressure. Compound **6** was obtained as a yellow solid (11.7 g, 100%) and used in the next step without further purification.



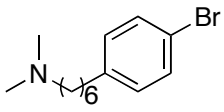
A.1.3 1-(4-Bromophenyl)-6-(*N*,*N*-dimethylamino)hexan-1-one (7)

The preparation of **7** has been adapted from a previously published procedure.[62] Anhydrous aluminum chloride (18.0 g) was added to a stirred solution of **6** (11.7 g, 75.0 mmol) in bromobenzene (60 mL) at 0 °C. After stirring at 50 °C for 2 h, ice water (100 mL) and aqueous hydrochloric acid (14.0 mL, 6.0 M) was added to the reaction mixture and stirred at room temperature for 12 h. After adjusting the pH of the mixture to above 12 with aqueous sodium hydroxide (2.0 M), the mixture was extracted with dichloromethane (3 × 100 mL), washed with a saturated aqueous solution of sodium chloride (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (10:1:0.2 ethyl acetate/methanol/triethylamine) gave **13** as a white solid (50%). ^{1}H NMR ($CDCl_3$, δ): 1.32(m, 4H, CH_2), 1.44 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.20 (s, 6H, CH_3), 2.26 (t, J = 7.3 Hz, 2H, CH_2), 2.55 (t, J = 7.6 Hz, 2H, CH_2), 7.00–7.08 (m, 2H, Ar H), 7.34–7.42 (m, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 27.2, 27.4, 29.2, 31.4, 35.5, 45.2, 59.7, 119.5, 130.4, 131.5, 199.2.



A.1.4 6-(4-Bromophenyl)-*N*,*N*-dimethyhexan-1-amine (8)

The preparation of **8** has been adapted from a previously published procedure.[62] Compound **7** (9.00 g, 33.0 mmoL) and hydrazine monohydrate (5.90 g, 118 mmol) were added to a stirred suspension of potassium hydroxide (5.30 g, 94.3 mmol) in triethylene glycol (40 mL). The reaction mixture was stirred at 135 °C for 3 h and then at 195 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with water (18 mL) and aqueous hydrochloric acid (8.0 mL, 6.0 M) and then stirred overnight. After adjusting the pH of the mixture to above 11 with a saturated aqueous solution of sodium carbonate, the mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (10:1:0.1 ethyl acetate/methanol/triethylamine) gave pure **8** as a pale yellow oil (5.2 g 58%). ^{1}H NMR ($CDCl_3$, δ): 1.32(m, 4H, CH_2), 1.44 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.20 (s, 6H, CH_3), 2.26 (t, J = 7.3 Hz, 2H, CH_2), 2.55 (t, J = 7.6 Hz, 2H, CH_2), 7.00–7.08 (m, 2H, Ar H), 7.34–7.42 (m, 2H, Ar H). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 27.2, 27.4, 29.2, 31.4, 35.5, 45.2, 59.7, 119.5, 130.4, 131.5, 141.8.


Br
N
6